# FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF INTRA GASTRIC FLOATING DRUG DELIVERY SYSTEM OF OFLOXACIN

**A Dissertation Submitted to**

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**In partial fulfillment for the award of Degree of**

**MASTER OF PHARMACY (Pharmaceutics)**

**Submitted by**


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**Under the Guidance of**


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**(ACCREDITED BY ''NAAC'' WITH A CGPA OF 2.74 ON A FOUR POINT SCALE AT ''B'' GRADE)**

**MELMARUVATHUR - 603 319**


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# CERTIFICATE

This is to certify that the research work entitled "**FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF INTRA GASTRIC FLOATING DRUG DELIVERY SYSTEM OF OFLOXACIN"** submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **"RAVALI VEDULLA" (Register No. 26106017)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2011-2012.

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# CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION DEVELOPMENT AND *IN VITRO* EVALUATION OF INTRA GASTRIC FLOATING DRUG DELIVERY SYSTEM OF OFLOXACIN"** the bonafide research work carried out by **"RAVALI VEDULLA" (Register No. 26106017)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the guidance of **Mr. T. AYYAPPAN,** M. Pharm., Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, during the academic year 2011-2012.

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**Place: Melmaruvathur**
**Date:**

*Dedicate to*

*my beloved parents...*

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**RAVALI VEDULLA**

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# ABBREVIATIONS

| | | |
|---|---|---|
| % | _ | Percentage |
| ºC | _ | Degree Celsius |
| µg | _ | Microgram |
| $\lambda_{max}$ | _ | Absorption maximum |
| BP | _ | British Pharmacopoeia |
| CDDS | _ | Controlled drug delivery system |
| CRDF | | Controlled release dosage form |
| CR | _ | Controlled release |
| Cm | _ | Centimeter |
| DE | _ | Dissolution efficiency |
| DNA | | Deoxy Ribonucleic acid |
| DSC | _ | Differential scanning calorimetry |
| F | _ | Formulation |
| FDDS | _ | Floating drug delivery system |
| FTIR | _ | Fourier Transform-Infra Red Spectroscopy |
| GET | _ | Gastric emptying time |
| GIT | _ | Gastro intestinal tract |
| GRDF | _ | Gastro retentive dosage forms |
| HBS | _ | Hydrodynamically Balanced System |
| HCL | _ | Hydrochloride |
| HCl | _ | Hydrochloric acid |

| | | |
|---|---|---|
| HPMC | _ | Hydroxy Propyl Methyl Cellulose |
| IP | _ | Indian Pharmacopoeia |
| ICH | _ | International conference on harmonization |
| LOD | _ | Loss on drying |
| rpm | _ | Revolutions per minute |
| M | _ | Slope, unit of response |
| MDT | _ | Mean dissolution time |
| MMC | _ | Migrating myoelectric complex |
| MP | _ | Melting point |
| MRT | _ | Mean residence time |
| N | _ | Normality |
| nm | _ | Nanometer |
| ppm | _ | Parts per million |
| RH | _ | Relative humidity |
| SD | _ | Standard deviation |
| UV-VIS | _ | Ultraviolet- visible |
| < | _ | Less Than |
| > | _ | More Than |

# INTRODUCTION

# 1. INTRODUCTION

## 1.1. ORAL DRUG DELIVERY SYSTEM

**(***Brahmankar D.M. and Jaiswal S.B., 2009; Robinson J.R. and Lee V.H.L., 2005)*

Oral drug delivery has been known for decades as the most widely used route of administration among all the routes. Oral delivery of drugs is the most preferable route of drug delivery due to ease of administration, patient compliance and flexibility in formulation. Pharmaceutical product designed for oral delivery which are currently available in the market mostly immediate-release or conventional release, which maintains the drug concentration within the therapeutically effective range only, when administered several times a day. This results in a significant fluctuation of drug level in plasma.

An ideal dosage regimen in the drug therapy of any disease is the one which immediately attains the desired therapeutic concentration of drug in plasma (or at site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at particular frequency. The frequency of administration or dosing interval of any drug depends upon its half-life or mean residence time (MRT) and its therapeutic index. In most cases, dosing interval is shorter than the half-life of the drug resulting in a number of limitations associated with such a conventional dosage form.

## 1.2. ORAL CONTROLLED DRUG DELIVERY SYSTEM

**(***Brahmankar D.M., 2009; Jain N. K., 2008)*

Oral controlled release dosage forms (CRDF) have been extensively used to improve therapy of many important medications. The design of oral controlled drug delivery systems (CDDS) should primarily be aimed at achieving more predictable and increased bioavailability of drugs. However, the developmental process is precluded by several physiological difficulties, such as inability to restrain and locate the CDDS within desired regions of gastrointestinal tract (GIT) due to the variable gastric emptying and motility. The variability may lead to unpredictable time for peak plasma levels and bioavailability. Therefore, the CRDF approaches has not been suitable for a variety of important drugs, characterized by a narrow absorption window in the upper part of the GIT, i.e. stomach and small intestine, which is due to relatively short transit time of the dosage form in these anatomical segments. Thus within a short period (less than 6 hours), the CRDF of such drugs leave the upper part of GIT and reaches to the non-absorbing distal segment, eventually resulting in a short absorption phase accompanied with lesser bioavailability.

Invariably, conventional dosage forms do not maintain the drug blood levels within the therapeutic range for an extended period of time. To achieve the same, a drug may be administered repeatedly using a fixed dosing interval. This causes a several potential problems like saw tooth kinetics characterized by large peaks and troughs in the drug concentration-time curve

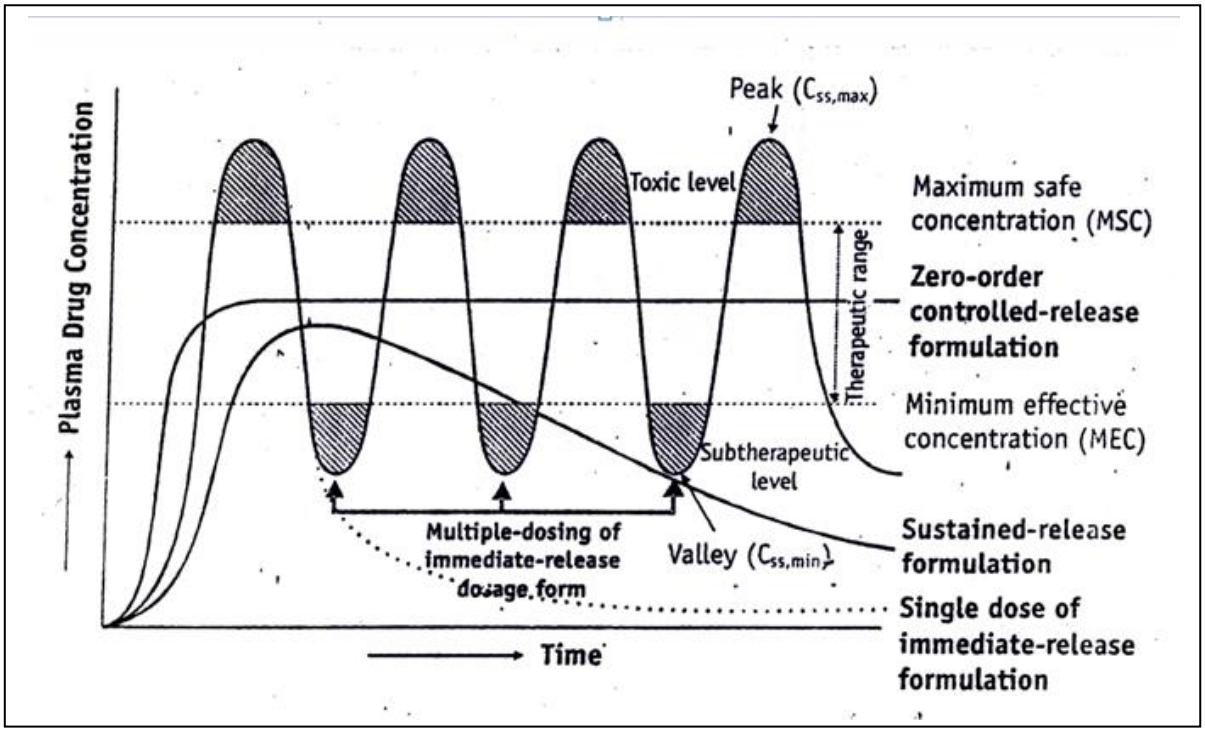



**Fig 1.1:** A hypothetical plasma drug concentration-time profile from conventional multi dosing and an ideal controlled delivery formulation

The relatively brief gastric emptying time in humans normally averages 2 to 3 hours. Through the major absorption zone (stomach or upper part of the intestine), which can result in incomplete drug release from the drug delivery system in a specific region of the GIT offers numerous advantages, especially to the drugs having narrow absorption window in GIT, primary absorption in the stomach stability problem in the intestine, poor solubility at alkaline $P^H$ , local activity in the stomach and property to degrade in colon. Compounding the drugs with narrow absorption window enable an extended absorption phase of these drugs.

One of the most feasible approaches for achieving a prolonged and predictable drug delivery profiles in the GIT is to control the gastric residence time, using gastroretentive dosage forms (GRDF).GRDF are the drug delivery systems that are

designed to be retained in the stomach for a prolonged time and release their active materials and thereby enable sustained input of the drug to the upper part of the GIT. This technology has generated enormous attention over the last few decades owing to its potential retention in the upper GIT can greatly improve the oral delivery of some important drugs for which prolonged retention in the upper GIT can greatly improve their oral bioavailability and/or their therapeutic outcome.

In the last three decades various attempts have been made to develop a novel and efficient gastro-retentive dosage forms which can retain in the stomach for an extended period of time in a predetermined manner. This can be achieved by improving scientific and technological advancement to overcome physiological problems like $P^H$ of the stomach, motility and gastric emptying time by altering physiological and formulation variables. Many approaches are utilized in the development of gastric retention drug delivery systems viz., floating systems, swelling, expanding, high density, super porous hydro gels, bioadhesive, modified shape systems, ion exchange resin and by the simultaneous administration of pharmacological agents that delay gastric emptying. By utilizing one of these techniques it is possible to deliver drugs that have narrow absorption window.

From the formulation and technological point of view, the floating drug delivery system (FDDS) is considerably easy and logical approach in the development of GRDF. Floating drug delivery system float on the gastric fluid only when it has density less than that of gastric fluids, i.e. <1 $g/cm^3$. Usually, floating formulations are prepared from hydrophilic matrices that either have a density lower than one or their density drops below one after immersion in the gastric fluids owing to swelling. More sophisticated

devices are developed later and involved in the use of various film coating techniques, incorporation of a floating chamber that is filled with harmless gas, or a liquid that gasifies at body temperature. These systems are often called hydro-dynamically balanced system (HBS) as they can maintain low density and keep floating even after hydrating. This system provides several advantages as prolonged gastric retention of drugs, improves bioavailability, reduces drug wastage and improves solubility for drugs that are less soluble in an alkaline $P^H$ environment and provides local drug delivery to the stomach and proximal small intestine.

## 1.3. ANATOMY AND PHYSIOLOGY OF STOMACH

*(Ross and Wilson;2006 )*

Stomach is an organ with capacity for storage and mixing. It is located just below the diaphragm in the epigastric and left hydrochondriac region of the abdomen.

The stomach is anatomically divided into three parts:

- Fundus
- Body
- Pylorus (Or antrum)

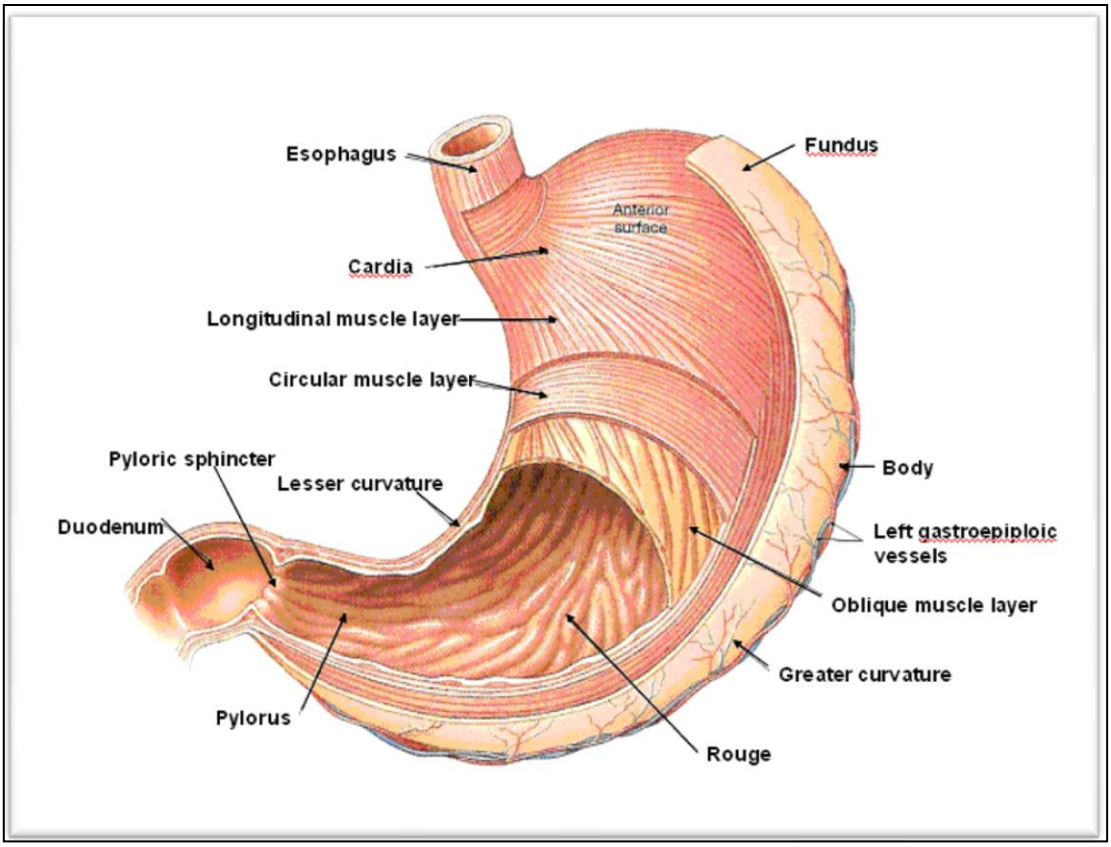



**Fig 1.2:** It shows structure of stomach

Stomach is made up of fundus and body regions. They are capable of displaying a large expansion to accommodate food without much increase in intragastric pressure.

Stomach lining is devoid of villi and it consists of considerable number of gastric pits that contribute to storage capacity of the stomach. Ant rum region is responsible for the mixing and grinding of gastric content. There are two main secretions: mucus and acid, produced by specialized cell in stomach lining. Mucus is secreted by goblet cells and gastric acid by parietal cells (oxyntric) The Mucus spread and cover the rest of GI tract. Under fasting condition the stomach is a collapsed bag with a residual volume of 50 ml and contains a small amount of gastric fluid (pH 1-3) and air.

- **Physiology:**

The physiology and disease state of stomach has a direct effect on design of controlled drug delivery system because drug is absorbed from and enters into site of action. Factors such as pH, nature and volume of gastric secretions and gastric mucosa play an important role in drug release and absorption.

**Table 1.1:** Table shows anatomical difference between different regions of the GIT

| **Particulars** | **Stomach** | **Small intestine** | **Large intestine** | **Rectum** |
|---|---|---|---|---|
| pH range | 1-3 | 5-7.5 | 7.9-8.0 | 7.5-8.0 |
| Length (cm) | 20 | 285 | 110 | 20 |
| Diameter (cm) | 15 | 2.5 | 5 | 2.5 |
| Surface area(sq.m) | 0.1-0.2 | 200 | 0.15 | 0.02 |
| Blood flow(L/min) | 0.15 | 1.0 | 0.02 | - |
| Transit time (hrs) | 1-5 | 3-6 | 6-12 | 6-12 |

- **pH:**

Environmental pH affects the performance of orally administered drugs. The pH of stomach in fasted condition is about 1.5 to 2 and in fed conditions it is usually 2 to 6. A large volume of water administered with oral dosage form changes the pH of stomach to pH of water initially. This change occurs because stomach does not have enough time to produce sufficient quantity of acid before emptying of liquid from the stomach.

- **Volume:**

The resting volume of stomach is about 25-52 ml. Gastric volume is important for dissolution of the dosage forms *in-vivo.* Meyer et al. conducted an experiment to study the effect of gastric fluid volume on absorption of controlled release theophylline dosage form in human beings. During this experiment they measured the gastric fluid volume of each subject. They estimated the mean gastric fluid volume in normal and achlorhydric subjects. The mean volume recovered by gastric aspiration over three consecutive, 15 min. time periods was 61+ 51 ml in achlorhydric subjects and 98+38 ml in normal subjects. Thus, there is such a large volume difference in gastric secretions that would significantly affect *in-vivo* dissolution of drugs.

- **Gastric mucosa:**

Simple columnar epithelial cells line the entire mucosal surface of the stomach. Mucus, parietal and peptic cells are present in the body of stomach. These cells are associated with different functions. The parietal cells secrete acid whereas the peptic cells secrete precursor for pepsin. The surface mucosal cells secrete the mucus and bicarbonate. They protect the stomach from digestion by pepsin and from the adverse effects of hydrochloric acid. As mucus has lubricating effect, it allows chyme to move freely through the digestive system.

- **Gastric secretion:**

Acids, pepsin, gastrin, mucus and some other enzymes are the secretions of the stomach. Normal adults produce a basal secretion up to 60 ml with

approximately 4 milli mol of hydrogen ions every hour. Other potent stimulators of gastric acid are the hormones like gastrin, peptides, amino acids and gastric distention.

- **Liquid In fasted and fed conditions**:

  Volumes of liquids affect gastric emptying of liquids, larger the volume, faster the emptying. Gastric emptying of small volumes like 100 ml or less is governed by the MMC cycle whereas large volumes of liquids 200 ml or more are emptied out immediately after administration.

- **Effect of food on gastric secretion:**

  Type of meal and its caloric content, volume, viscosity and co-administered drugs affect gastric secretions and gastric emptying time. The rate of emptying primarily depends on caloric contents of the ingested meal. It does not differ for proteins, fats and carbohydrates as long as their caloric contents are the same.

➢ **Gastric motility:** *(Jain N.K., 2008)*

The pattern series of motility is distinct in fasted and fed states. During the fasting state an inter digestive series of electrical events takes place, which cycle both through stomach and intestine every 2 to 3 hrs. This is called the interdigestive

myoelectric cycle or migrating myoelectric cycle (MMC), which is divided into following 4 phases**.**

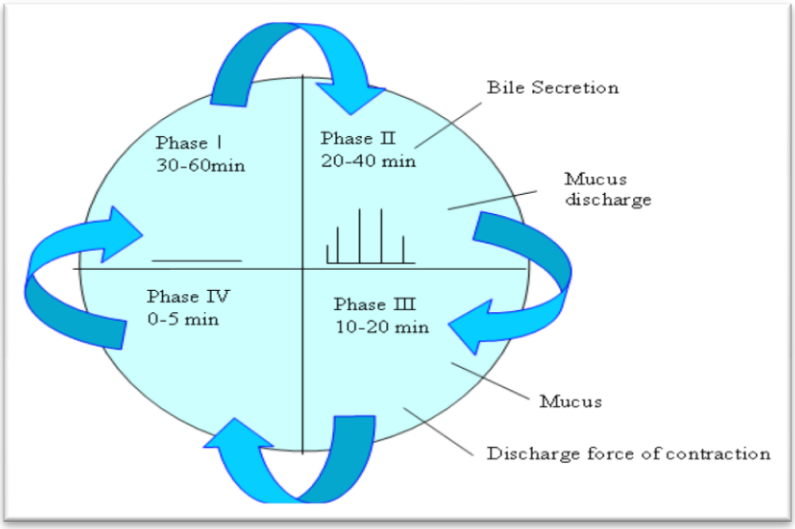



**Fig. 1.3:** It shows the four phases of myoelectric cycle

- Phase I (basal): Lasts for 30 to 60 minutes. Contractions can be characterized by a lack of secretary, electrical, and contractile activity.
- Phase II (preburst): Lasts for 20 to 40 minutes. With intermittent action potential and contractions.
- Phase III (burst): Lasts for 10 to 20 minutes. Includes intense and regular contractions. It is due to this wave that all undigested material is swept out of the stomach down to the small intestine. It is also known as housekeeper wave.
- Phase IV: Lasts for 0 to 5 minutes.

After the ingestion of mixed meal, the pattern of contractions changes from fasted to fed state. It comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (<1mm), which are propelled toward pylorus. During fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.

- **Gastric emptying:** *(Jain N.K., 2008)*

It can be anticipated that, depending upon the physiological state of subject and design of pharmaceutical formulation, the emptying process last from a few minute to 12 hours. Furthermore the relatively brief gastric emptying time in humans which normally averages 2 to 3 hours through the major absorption zone (stomach or upper part of intestine). Particle size and feeding state strongly affect the residence time of particles in the stomach. Some other factors affecting gastric emptying are type of meal and its caloric content, volume, viscosity and co-administered drugs. The rate of gastric emptying primarily depends on the caloric contents of the ingested meal. It does not differ for proteins, fats, and carbohydrates as long as their caloric content is the same. Generally an increase in acidity, osmolarity and caloric value slows down gastric emptying. Stress increases gastric emptying rate whereas depression slows it down. Females have a slower gastric emptying rate than males. Age and obesity also effect gastric emptying

**Table. 1.2:** Shows transit time of stomach and small intestine with different dosage forms

| **DOSAGE FORMS** | **TRANSIT TIME(HOURS)** | | |
|---|---|---|---|
| | STOMACH | SMALL INTESTINE | TOTAL |
| TABLETS | 2.7 | 3.1 | 5.8 |
| PELLETS | 1.2 | 3.4 | 4.6 |
| CAPSULES | 0.8 | 3.2 | 4.0 |
| SOLUTION | 0.3 | 4.1 | 4.4 |

- **Factors affecting gastric emptying time:**

*(Vyas S., 2009; Bandyopadhyay A.K., 2008)*

- **Volume:**

The resting volume of stomach is about 25 to 52ml. This volume is important for dissolution of dosage forms. As the volume is large, emptying is faster. Gastric emptying of small volumes like 100ml or less is governed by MMC cycle where as large volumes of liquids like 200ml or more are emptied out immediately after administration. Fluids at body temperature leave the stomach more rapidly than either warmer or colder fluids.

- **Harmonal effects:**

Stress condition increases gastric emptying rate where as depression slows down gastric emptying time. Generally females have slower gastric emptying rate than males. Age and obesity also affect gastric emptying.

- **Presence of food:**

Gastric emptying time differs in fasted state and in fed state. The caloric value of food affects the gastric emptying time.

- **Gastric secretions:**

Acids, pepsin, gastrin, mucus and other enzymes and other enzymes are the secretions of stomach. Normal adults produce a basal secretion upto 60ml with approximately 4 millimoles of hydrogen ions every hour.

- **Factors affecting gastric residence time of dosage form:**

*(Vyas S., 2008; Bandyopadhyay A.K.,2008)*

- **Density:**

Gastric residence time increases if the density of the dosage form is less than the gastric contents (<1.004 gm/ml).

Size and shape:

Small-size tablets leave the stomach during the digestive phase while the large size tablets are emptied during the housekeeping waves.

- **Fed or unfed state:**

Under fasting conditions, the GI motility is characterized by periods of MMC that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulations coincides with that of the MMC, the gastric residence time of the unit can be expected to be very short. However, in the fed state, MMC is delayed and gastric residence time is considerably longer.

- **Frequency of feed:**

The gastric residence time can be increased by over 400 minutes when successive meals are given compared with a single meal due to the lower frequency of MMC.

- **Posture:**

Gastric residence time can vary between supine and upright ambulatory state of the patients

- **Concomitant drug administration:**

Anticholinergics like atropine and propentheline, opioids like codeine and prokinetic agents like metoclopromide and cisapride affects the GRT when administered together.

- **Biological factors:**

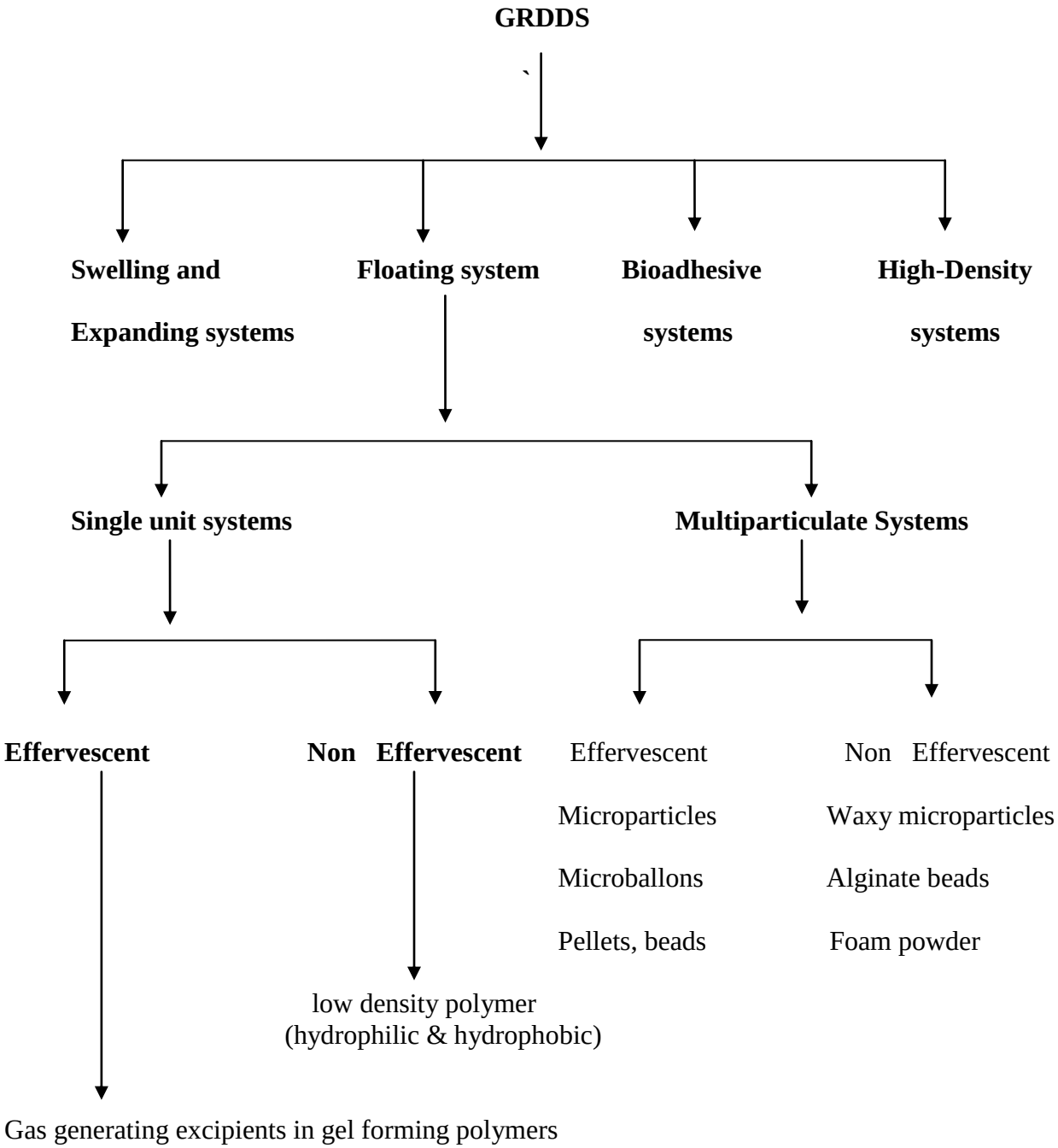
Diabetes and crohn's disease also affects gastric residence time.

### 1.3.1. Formulation approaches for gastro retentive drug delivery system

*(Garg R., 2008)*

There are several formulation approaches used for designing gastro retentive drug delivery systems. These include swelling and expanding system, which are retained in the gastric region due to their large size gained after swelling. Floating system is retained in the gastric region due to their floating ability on the gastric fluid. The floating system is further divided into single unit system such as floating tablets and multiparticulate systems such as floating microspheres, which offer more advantages as compared to single unit system. The floating system is further divided into effervescent and non-effervescent floating system based on their mechanisms of floating. Bioadhesive systems adhere to the gastric mucosa due to which they are retained in the gastric region. High density systems are retained due to their increased density then the gastric fluid. Beside this, passage delaying food as well drugs can be administered simultaneously to retained the dosage form in the gastric region.

The flowchart shows the various approaches used to retain the dosage forms in the gastric region.



- **Swelling and expanding systems:**

Swelling type dosage forms are such that after swallowing , these products swell to an extent that prevents there exit from the stomach through the pylorus . As a result, the dosage form is retained in the stomach for a long period of time. These systems may be referred to as 'plug type ' systems since they exhibit tendency to remain lodged at the pyloric sphincter.

- **Floating system (low density approach)**

These systems are also known as hydro–dynamically balanced systems. (HBS/FDDS) they have a bulk density lower than gastric fluid, i.e. their bulk density is less than one. The specific gravity of gastric fluid is approximately 1.004 to1.010 gm/cm$^3$ and thus the FDDS remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on gastric contents the drug is released slowly at a desired rate from the system. After the release of the drug the residual system is emptied from the stomach.

- **Bioadhesive system:**

They are used to localize a delivery device within the lumen and cavity of the body to enhance the drug absorption process in a site-specific manner. It makes use of bioadhesive polymers. These polymers tend to form hydrogen and electrostatic bonds at the mucus polymer boundary.

- **High density systems:**

High density formulations include coated pellets that have density greater than that of stomach contents. (>1.004g/cm$^3$) This is accomplished by coating the drug

with heavy inert materials such as barium sulfate, titanium dioxide, iron powder or oxide. The weighed pellet can be covered with a diffusion-controlling polymer membrane.

- **Modified shape systems:**

These are non-disintegrating geometric shapes molded from silastic elastomer or extruded from polyethylene blends which extend the gastric residence time depending on size and shape of the dosage form.

**1.3.1.1. Use of other delayed gastric emptying device:**

It includes feeding of ingestible polymers or fatty acid salts that change the motility pattern of the stomach to a fed state, thereby decreasing the gastric emptying rate and permitting considerable prolongation of drug release.

- **Osmotic regulated system:**

It is comprised of an osmotic pressure controlled drug delivery device and an inflatable floating support in a bioerodable capsule. In the stomach the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable support inside forms a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. The osmotic pressure controlled drug delivery consists of two components are as drug reservoir compartment and osmotically active compartment.

- **Incorporation of passage delaying food agents:**

The food excipients like fatty acids, e.g. salts of myristic acid change and modify the pattern of the stomach to a fed state, there by decreasing gastric emptying rate and permitting considerable prolongation of release. The delay in the gastric emptying after meals rich in fats is largely caused by saturated fatty acids with chain of C10 to C14.

- **Ion exchange resin:**

A coated ion exchange resin bead formulation has been shown to have gastric retentive properties, which was loaded with bicarbonates. Ion exchange resins are loaded with bicarbonate and a negatively charged drug is bound to the resin, resultant beads were then encapsulated in a semi-permeable membrane to overcome the rapid loss of carbon dioxide. Upon arrival in the acidic environment of the stomach and exchange of chloride and bicarbonate ions take place. As a result of this reaction carbon dioxide was released and trapped in a membrane thereby carrying beads towards the top of gastric content and producing a floating layer of resin beads in contrast the uncoated beads which will sink quickly

## 1.4. TECHNOLOGICAL DEVELOPMENT IN FDDS

*(Bandyopadhyay A.K., 2008; Patil J.M., et al., 2006)*

Based on the mechanism of buoyancy, two distinctly different types, i.e. non-effervescent and effervescent systems have been utilized in the development of FDDS.

### A. Effervescent FDDS:

Effervescent system utilize matrices prepared with swellable polymers such as methocel or polysaccharides e.g., chitosan and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of dosage form and maintains its buoyancy.

**a. Multiple-unit oral floating drug delivery system:**

Recently a multiple–unit type of floating pill, which generates carbon dioxide gas, has been developed. The system consisted of sustained–release pills as seeds surrounded by double layers. The inner layer an effervescent layer containing both sodium bicarbonate and tartaric acid. The outer layer was a swellable membrane layer containing mainly polyvinyl acetate and purified shellac. Moreover, the effervescent layer was divided into two sub layers the sodium bicarbonate was contained in the inner sub layer and tartaric acid was in the outer layer.

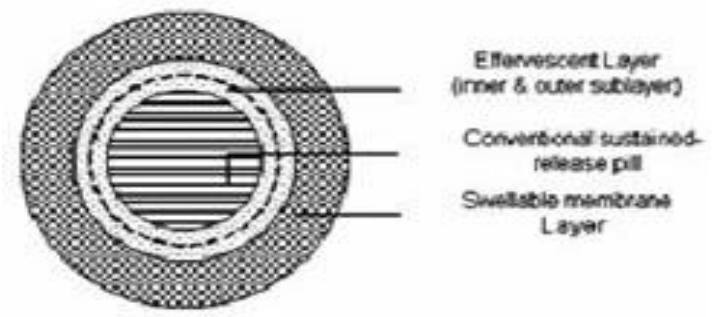



**Fig 1.4:** It shows multiple unit oral floating drug delivery system

When the swollen pills are formed, like balloons, they have a density much lower than 1.004 gm/cm$^3$. The reaction was due to carbon dioxide generated by neutralization in the inner effervescent layer with the diffusion of water through the outer swellable membrane layer.

A floating system utilizing ion-exchange resins has been developed. The system consisted of resin beads, which were loaded with bicarbonate and a negatively charged drug that was bound to the resin. The resultant beads were then encapsulated in a semi permeable membrane to overcome rapid loss of carbon dioxide. Upon arrival in the acidic environment of stomach, an exchange of chloride and bicarbonate ion takes place, as it is

expected. As result of this reaction, carbon dioxide was released and trapped in the membrane, thereby, carrying beads toward the top of gastric contents and producing a floating layer of resin beads. In contrast, the uncoated beads sink quickly. Radioactivity measurement by scintigraphy showed that gastric residence was substantially prolonged, compared with a control, when the system was given after a light, mainly liquid meal.

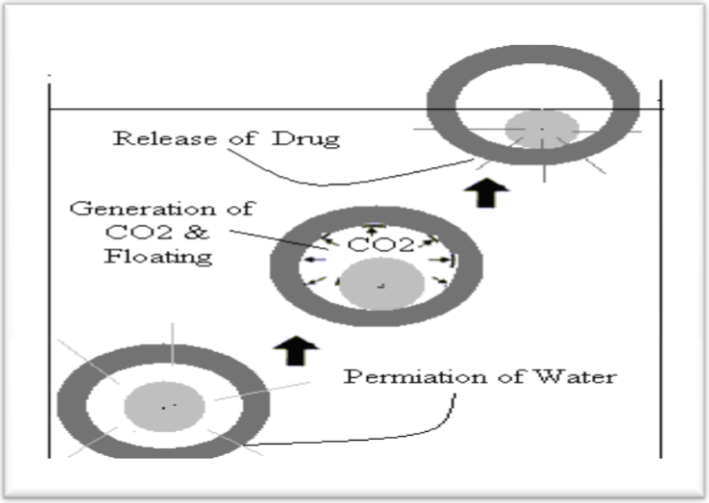



**Fig 1.5:** It shows mechanism of effervescent drug delivery system

Furthermore, the system was capable of slow release of drug, a Property which widens the scope of such floating system for SR preparation of drugs possessing negative charge since they can be easily bound to the resin in combination with bicarbonate ions. Two patents on FDDS issued to the Alza Corporation disclosed drug delivery devices for the controlled and continuous administration of medicinal agents. Following figure shows mechanism of floating of effervescent drug delivery system.

**b. Inflatable gastrointestinal drug delivery system:**

The residence time of the drug delivery device in the stomach can also be

sustained by incorporation of an inflatable chamber, which contains a liquid, e.g., ether that gasifies at body temperature to cause the chamber to float in the stomach.

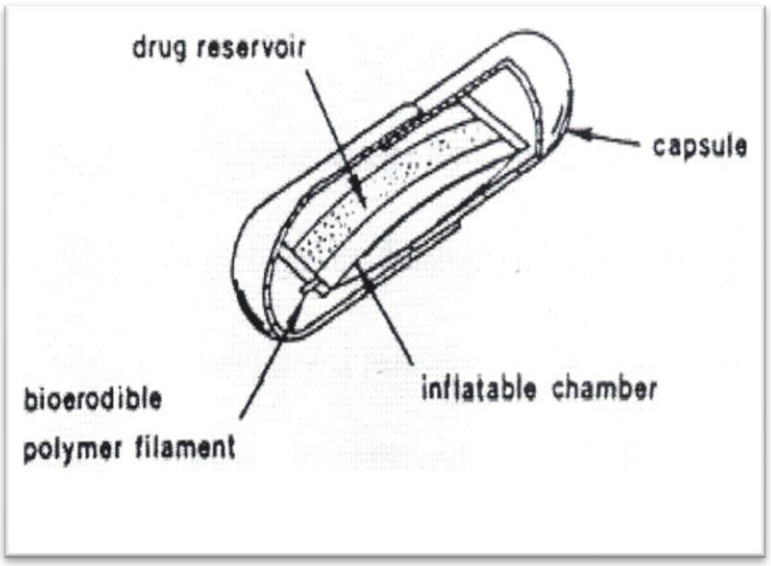



**Fig 1.6:** It shows inflatable gastrointestinal drug delivery device

**c. Intragastric osmotically controlled drug delivery system:**

It is comprised of an osmotic pressure controlled drug delivery and an inflatable floating support in a bio-erodible capsule. When the drug delivery device reaches the site of drug administration e.g. the stomach, the capsule quickly disintegrates to release the intragastric osmotically controlled drug delivery device. The inflatable floating support is made from a deformable hollow polymeric bag that contains a liquid that gasifies at body temperature to inflate the bag. Although single unit floating dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing emptying process while the multiple unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus, release the drug more uniformly.

The uniform distribution of these multiple unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritation; this gave birth to oral controlled drug delivery and led to development of gastro-retentive floating microspheres.

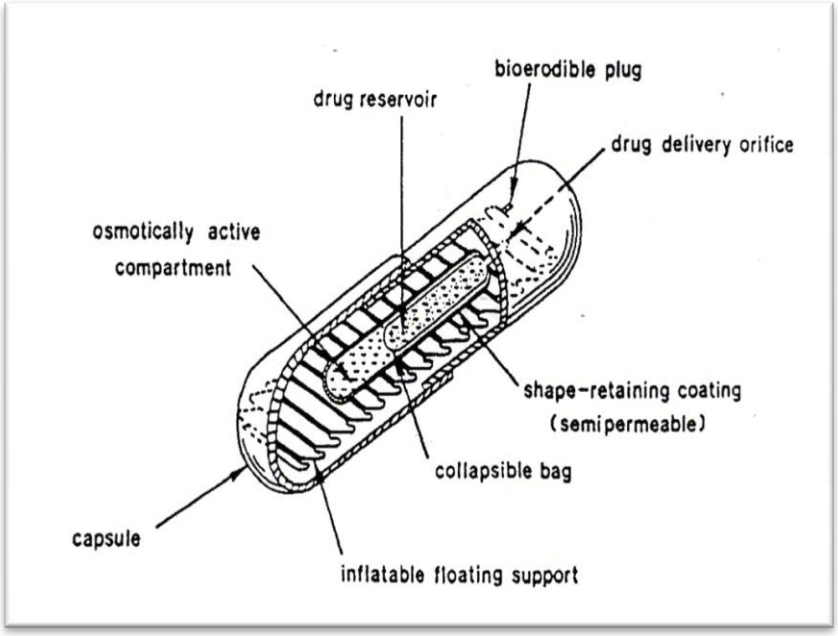



**Fig 1.7:** It shows intragasric osmotically controlled drug delivery device.

## B. NON-EFFERVESCENT FDDS

Floating microsphere are gastro-retentive delivery systems based on non-effervescent approach. Gastro-retentive floating microspheres are low density systems that have sufficient buoyancy to float over gastric contents and remain in stomach for prolonged period. As the system floats over gastric contents, the drug is released slowly at desired rate resulting increased gastric retention with reduced fluctuations in plasma drug concentration. Hollow microspheres are prepared by solvent diffusion and evaporation methods to create the hollow inner core.

**a. Hydro dynamically balanced intragastric delivery system**

The hydro dynamically balanced gastrointestinal drug delivery systems, in either capsule or tablet form, is designed to prolong GI residence time in an area of the GI tract to maximize drug reaching its absorption site in solution state and hence, ready for absorption. It is prepared by incorporating a high level (20-75% w/w) of one or more gel-forming hydrocolloids e.g. hydroxyl ethylcellulose, hydroxypropyl cellulose, hydroxyl propyl methyl cellulose and sodium carboxy methyl cellulose into the formulation and then compressing these granules into a tablets.

On contact with gastric fluid the hydrocolloid in this intragatric floating device start to become hydrated and forms a colloid gel barrier around its surface with thickness growing with time. This barrier controls the rate of solvent penetration into the device and the rate of drug release from the device (Fig. 1.10). It maintains a bulk density of less than 1 and thus, remains buoyant in the gastric fluid inside the stomach for up to 6 hours.

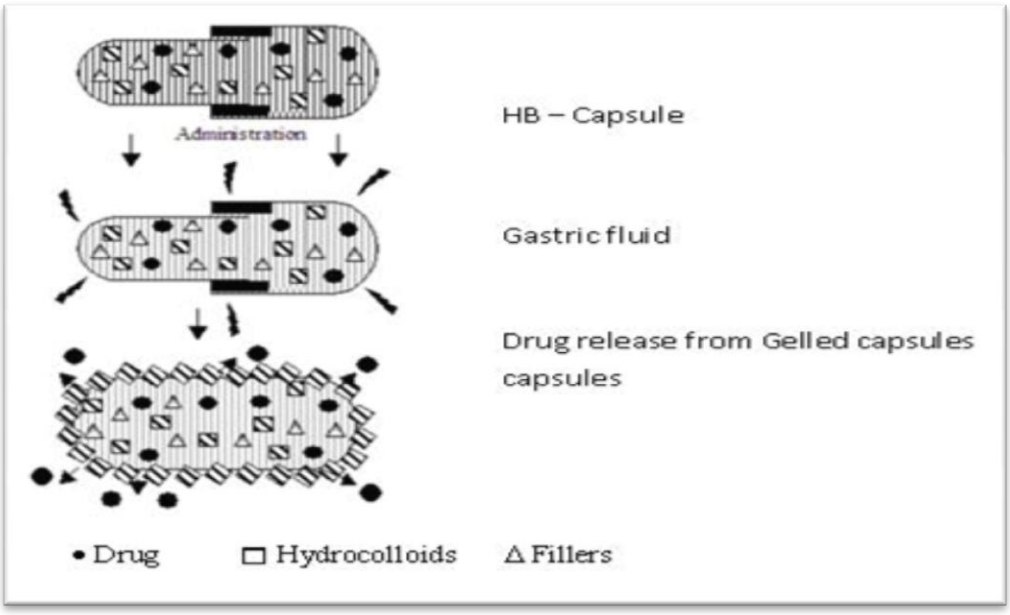



**Fig 1.8:** It shows working principle of hydrodynamically balance system

**b. Bilayer tablet:**

A bilayer tablet can be prepared to contain one immediate–release layer and one sustained–release layer. After the initial dose is delivered by the immediate release layer, the sustained layer absorbs the gastric fluid and forms a colloidal gel barrier on its surface. This produces a bulk density less than that of the gastric fluid and release remains buoyant in the stomach for extended period of time.

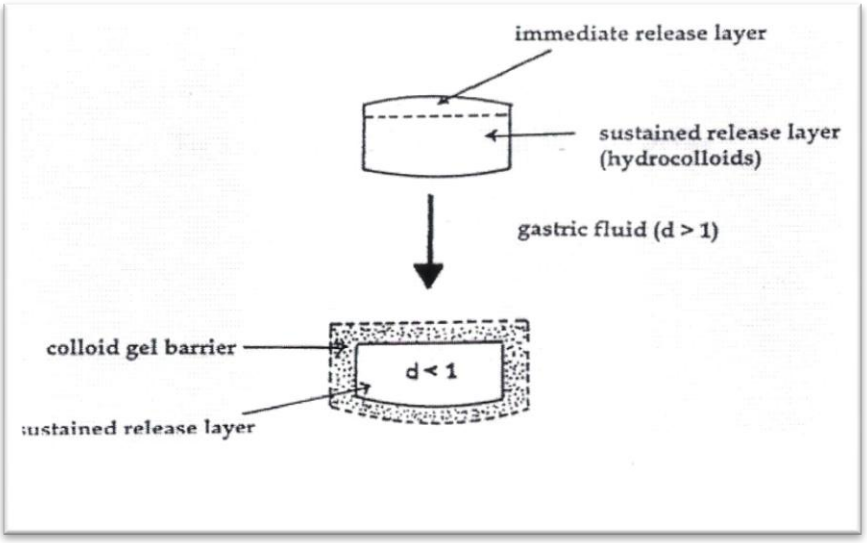



**Fig 1.9:** It shows intragastric floating bilayer tablet

**c. Intragastric floating gastrointestinal drug delivery system**:

A gastrointestinal drug delivery system can be made to float in the stomach by incorporating a floatation chamber, which may be a vacuum or filled with a harmless gas.

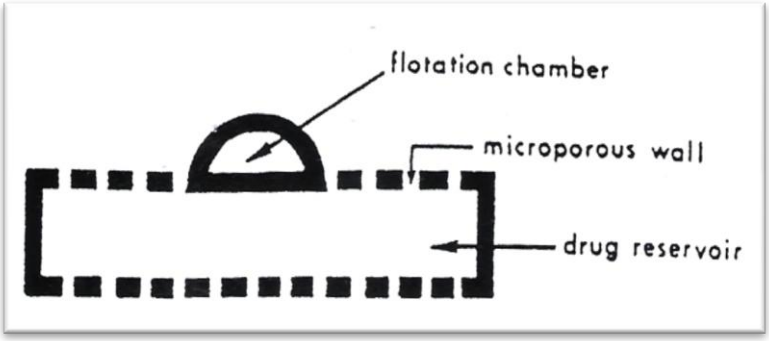



**Fig 1.10:** It shows intra-gastric floating drug delivery device

A drug reservoir is encapsulated inside a micro-porous compartment with apertures along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the stomach mucosal surface with the un-dissolved drug. In the stomach the floatation chamber causes the gastrointestinal drug delivery system to float in the gastric fluids. Fluids enter through the apertures, dissolve the drug and carry and drug solute out of the drug delivery system for continuous transport to the intestine for absorption. The other two walls in contact with the fluid are sealed so that undissolved drug remains therein.

## 1.5. RECENT ADVANCES

### 1.5.1. Floating multi-layer coated tablets:

Floating multi-layer coated tablets were designed based on gas formation. The system consists of a drug -containing core tablet coated with a protective layer (hydroxypropyl methylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane respectively. The acrylic polymers Eudragit and ethyl cellulose

were suitable film for the system, and was chosen as gas-entrapped membrane due to its high flexibility and high water permeability.

**1.5.2. Raft System**

A gel–forming solution (e.g. sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped $CO_2$ bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminum hydroxide or calcium carbonate to reduce gastric acidity.

**1.5.3. Magnetic system**

This system is based on a simple idea that the dosage form contains a small internal magnet and a magnet placed on the abdomen over the position of stomach. The internal tablet guided by the oesophagus with an external magnet. These systems seem to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance.

**Criteria for selection of drug candidate for FDDS:**

**1)** Drugs required to exert local therapeutic action in the stomach e.g. Misoprostol, 5-Flurouracil, Antacids and anti-helicobacter pylori agents and certain enzymes.

**2)** Drugs exhibiting site-specific absorption in the stomach or upper part of small intestine. e.g. Atenolol, Levodopa, P-Aminobenzoic acid, piretanide, Salbutamol.

**3)** Drugs insoluble in intestinial fluids ( acid soluble basic drugs). e.g. Chlordiazepoxide, Chlorpheneramine, Cinnarzine,Diazepam, Diltiazem, Metaprolol, Propranolol, Verapamil.

**4)** Drugs with variable bioavailability. e.g. Sotalol hydrochloride and Levodopa**.**

**5)** Drugs unstable in lower part of GI tract. e.g. Captopril.

## 1.6. LIMITATIONS OF FDDS

*(Mayavanshi A.V. and Gajjar S.S., 2008)*

- The major limitation of floating system is requirement of a sufficient high level of fluids in the stomach for the drug delivery to float. However this limitation can be overcome by coating the dosage form with the help of bio-adhesive polymers that easily adhere to the mucosal lining of the stomach.
- Floating system is not feasible for those drugs that have solubility or stability problem in gastric fluids.
- Drugs which are irritant to gastric mucosa cannot be applicable to GRDFs, floating system.
- The residence time in the stomach depends upon the digestive state. Hence FDDS should be administered after the meal.
- The ability of drug to remain in the stomach depends upon the subject being positioned upright.
- The dosage form should be administered with a minimum of glass full of water (250 ml).

## 1.7. ADVANTAGES OF FDDS

*(Garg R. and Gupta G.D., 2008; Mayavanshi A.V, Gajjar S.S.2008)*

- It is advantageous for drugs absorbed through the stomach, for e.g. Riboflavin.

- It is not restricted to medicaments, which are absorbed from stomach, since it has been found that these are equally efficacious with medicaments which are absorbed from the intestine.
- It is advantageous for drugs meant for local action in the stomach, for e.g. antacids, antiulcer drugs.
- It reduces fluctuations in circulating blood level of drug as shown by the conventional dosage form.
- It shows more uniform levels of drug in plasma.
- It releases drug slowly and for prolonged period of time and hence reduces dosing frequency.
- It increases patient compliance as the dosing frequency is reduced.
- The dissolved drug gets available for absorption in the small intestine after emptying of the stomach contents. It is therefore expected that a drug will be fully absorbed from the floating dosage forms if it remains in the solution.
- Site specific drug delivery.
- Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon, hence minimizes adverse activity at the colon.

## 1.8. APPLICATIONS OF FLOATING DRUG DELIVERY SYSTEMS

*(Bandyopadhyay A.K., 2008; Mayavanshi A.V, Gajjar S.S.,2008)*

Floating drug delivery offers several applications for drugs having poor bioavailability because of the narrow absorption window in the upper part of the gastrointestinal tract.

- **Sustained Drug Delivery**

HBS systems can remain in the stomach for long periods and hence can release the drug over a prolonged period of time. The problem of short gastric residence time encountered with an oral CR formulation hence can be overcome with these systems. These systems have a bulk density of 1 as a result of which they can float on the gastric contents.

The sustained release floating capsules of nicardipine hydrochloride compared with commercially available MICARD capsules using rabbits. Plasma concentration time curves showed a longer duration for administration (16 hours) in the sustained release floating capsules as compared with conventional MICARD capsules (8 hours).

- **Site-Specific Drug Delivery**

These systems are particularly advantageous for drugs that are specifically absorbed from stomach or the proximal part of the small intestine, eg, furosemide.

It has been reported that a monolithic floating dosage form with prolonged gastric residence time was developed and the bioavailability was increased. AUC obtained with the floating tablets was approximately 1.8 times those of conventional furosemide tablets.

- **Absorption Enhancement**

Drugs that have poor bioavailability because of site specific absorption from the upper part of the gastrointestinal tract are potential candidates to be formulated as floating drug delivery systems, thereby maximizing their absorption.

A significant increase in the bioavailability of floating dosage forms (42.9%) could be achieved as compared with commercially available LASIX tablets (33.4%) and enteric coated LASIX-long product.

**Marketed preparations of FDDS:** *(Garg R., 2008)*

**Table1.3:** Marketed preparations of floating drug delivery system

| S. No. | Product | Active ingredients |
|---|---|---|
| 1 | Madopar | Levodopa & Benserazide |
| 2 | Valrelease | Diazepam |
| 3 | Topalkan | Aluminium magnesium |
| 4 | Almagate Flacoat | Antacid |
| 5 | Liquid Gavison | Alginic acid & bicarbonate |
| 6 | Conviron | Ferrous sulphate |
| 7 | Cifran OD | Ciprofloxacin |
| 8 | Cytocheck | Misoprostol |

# LITERATURE SURVEY

# 2. LITERATURE SURVEY

## 2.1. Literature Review:

1. **Ajit.K *et al*., (2009)** design bilayer regioselective floating tablets of atenolol and lovastatin to give immediate release of lovastatin and sustained release of atenolol. Bilayer floating tablets comprised two layers, i.e immediate release and controlled release layers. The immediate release layer comprised sodium starch glycollate as a super disintegrant and the sustained release layer comprised HPMC K100M and xanthan gum as the release retarding polymers. Sodium bicarbonate was used as a gas generating agent. Direct compression method was used for formulation of the bilayer tablets. Accelerated stability studies were carried out on the prepared tablets in accordance with ICH guidelines. All formulations floated for more than 12 h. More than 90% of lovastatin was released within 30 min. Diffusion exponents (n) were determined for all the formulations (0.53-0.59). The release of atenolol was found to follow a mixed pattern of Korsmeyer-Peppas, Hixson- Crowell and zero order release models. The optimized formulation was found to be buoyant for 8 h in stomach. Therefore, biphasic drug release pattern was successfully achieved through the formulation of floating bilayer tablets in this study.
2. **Anand.P *et al.*, (2009)** highlighted a novel gastro retentive controlled release drug delivery system of verapamil HCl was formulated in an effort to increase the gastric retention time of the dosage form and to control drug release. Hydroxypropylmethylcellulose (HPMC), carbopol, and xanthan gum were

incorporated for gelforming properties. Buoyancy was achieved by adding an effervescent mixture of sodium bicarbonate and anhydrous citric acid. In vitro drug release studies were performed, and drug release kinetics was evaluated using the linear regression method.

3. **Arora.S *et al.,* (2005)** The recent development of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single unit and multiple unit floating system, and their classification and formulation aspects are covered in detail. These systems are useful to several problems encountered during the development of dosage form.
4. **Basak.S.C *et al.,* (2004)** performed floating tablets of Ciprofloxacin for prolongation of gastric residence time, leading to an increase in drug bioavailability and sustained action. In-vitro drug release study of these tablets indicated controlled sustain drug release for Ciprofloxacin and 80 to 89% release at the end of the 8 hours.
5. **Baumgartner.S *et al.,* (2000**) described the matrix-floating tablet incorporating high dose of freely soluble drug. The formulation containing 54.7% of drug, HPMC K4 M, Avicel PH 101 and a gas-generating agent had given the best results. It required 30 seconds to become buoyant. In-vivo experiments with fasted state in beagle dogs revealed prolonged gastric residence time. On radiographic images taken after 30 minutes of administration, the tablet was observed in animal stomach and the next image taken at 1 hr showed that the tablet had altered its position and turned around. The comparison of gastric motility and stomach emptying between humans and dogs showed no big

difference hence it was speculated that the experimentally proven increased gastric residence time in dogs than humans.

6. **Brahma N. Singh *et al.*, (2000):**the future potential for oral controlled drug delivery was discussed and also added that technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as GRT, GET.
7. **Chandira.M *et al.*, (2009)** described that floating tablets of Diltiazem hydrochloride by direct compression technique using hydrophilic polymers like HPMC k4M, HPMC K15M and hydrophobic polymers like ethyl cellulose as matrix material in various quantities . It was concluded that F6 is the best formulation.
8. **Dalavi V.V *et al.*, (2009)** expressed that gastroretentive drug delivery system of an antiretroviral agent of Zidovudine to achieve the objective, 3×3 factorial design were chosen. In this design amount of HPMC K4M (X1) and gas generating agents (X2) were selected as independent variable. The time required for 50% drug release t50% (Y1) was selected as dependent variable. The derived polynomial equations for $t_{50}$%were verified by two check point formulations. The results of factorial design showed that factor X1 and X2 significantly affect the studied dependent variables. The formulation with good floating time (24hrs) and the percent drug release (98.05) emerged as optimal.
9. **Dave B.S *et al.*, (2004)** explained the floating tablet of ranitidine hydrochloride by using guar gum, xanthan gum and hydroxylpropyl methylcellulose, Sodium bicarbonate was incorporated as gas generating agent. It is prepared by direct

compression method and in-vitro study done into 0.1 N HCl as dissolution medium. Drug release was calculated by Higuchi and Peppas models.

10. **Dhawale S.C *et al.,* (2009)** had developed and evaluated floating drug delivery system of Acyclovir. Gastric floating drug delivery was employed to develop controlled release preparation. Sodium bicarbonte as gas generating agent dispersed in a hydrogel matrix. The matrix was a mixture of HPMC K4M, HPMC K100M and xanthan gum.
11. **Ganesh S *et al.,* (2008)** characterized the controlled release matrix tablets of zidovudine using hydrophilic HPMC K4 M or carbopol 934 alone or in combination with hydrophobic ethyl cellulose. The in-vitro drug release shows that formulation of HPMC K4 M or carbopol 934 with ethyl cellulose sustain the drug release for nearly 12 hours.
12. **Garg.R *et al*., (2009)** had prepared and evaluated floating tablets of silymarin as a model drug for prolongation of gastric residence time. Tablets were formulated by various materials like HPMC K4M, HPMC K15,Psyllium husk, Crosspovidone and gas generating agents like sodium bicarbonate and citric acid. The kinetics was found to follow both the higuchi and Korsermeyer-peppas equation. The floating tablets may be used in clinic for prolonged drug release for at least 24 hours.
13. **Hoffman.A *et al.,* (2003)** Expandable gastroretentive dosage forms (GRDFs) have been designed for the past 3 decades. They were originally created for possible veterinary use, but later the design was modified for enhanced drug therapy in humans. These GRDFs are easily swallowed and reach a significantly

larger size in the stomach due to swelling or unfolding processes that prolong their gastric retention time (GRT). Positive results were obtained in preclinical and clinical studies evaluating GRT of expandable GRDFs.

14. **Jaimini.M *et al.*, (2007)** formulated & evaluated floating tablets of Famotidine which were prepared by effervescent approach using two different grades of Methocel K100 and K15M. The tablets with Methocel K100 were found to float for longer duration as compared with formulations containing Methocel K15M. The drug release from the tablets was sufficiently sustained and non-Fickian transport of the drug from tablets was confirmed.
15. **J M Patil *et al.*, (2005):** discussed that several approaches are currently utilized in the prolongation of the GRT, including FDDS, swelling and expanding systems, polymeric bioadhesive systems, high density systems and other delayed gastric emptying devices.
16. **Kim H.K *et al.*, (2000)** has studied the scientific and technological advancements have been made in the research and development of rate-controlled oral drug delivery systems by overcoming physiological adversities, such as short gastric residence times (GRT) and unpredicta ble gastric emptying times (GET). Several approaches are currently utilized in the prolongation of the GRT, including floating drug delivery systems (FDDS), also known as hydrodynamically balanced systems (HBS), swelling and expanding systems, polymeric bioadhesive systems.
17. **Kishan.V *et al.*, (2009)** developed Floating matrix tablets of norfloxacin to prolong gastric residence time, leading to an increase in drug bioavailability.

Tablets were prepared by the wet granulation technique, using polymers such as hydroxypropyl methylcellulose (HPMC K4M, HPMC K100M) and xanthan gum.

18. **Mahesh Chavanpatil., *et al.,* (2005):** A new strategy is proposed for the development of gastroretentive dosage forms for Ofloxacin preferably once daily. The design was based on sustained release form. It was found that in vitro drug release rate increased with increased amount of crospovidone due to the increased water uptake, and hence increased driving force for drug release.
19. **Mayavanshi A.v *et al.,* (2008**) floating drug delivery system to increase gastric retention of drug: a review. Article studied the floating or hydrodynamically controlled drug delivery system are useful in gastric retention.
20. **Mina Ibrahim Tadros *et al.,* (2010):** selected ciprofloxacin hydrochloride which had a short elimination half-life, a narrow absorption window and is mainly absorbed in proximal areas of GIT. The purpose of this study was to develop a gastroretentive controlled release drug delivery system with swelling, floating, and adhesive properties using HPMC K15, Na alginate as polymers.
21. **Prajapati.S.T *et al.,* (2009)** developed gastric floating matrix tablet of Domperidone. Box-Behnken design was employed in formulating gastric floating drug delivery system using three polymers HPMC (K4M), Carbopol 934P, Sodium alginate as independent variables. HPMC loading was found to be significant for floating properties. No significant effect of Sodium alginate on floating properties was observed but it was important for gel formation. The quadratic mathematical model developed could be used to predict formulations with desired release and floating properties.

22. **Prakash. R *et al.,* (2009**) had formulated and optimized the floating drug delivery system containing cephalexin using 23 factorial designs. Floating tablets were prepared by direct compression method incorporating HPMC K4M,xanthan gum, guar gum, sodium bicarbonate and tartaric acid as gas generating agent. The influence of independent variables like, polymer ratio, polymer type and tartaric acid on floating lag time and cephalexin release profile were studied.
23. **Rajesh. K *et al.,* (2009)** formulated floating tablets of Ranitidine hydrochloride for prolongation of gastric residence time. Tablets of Ranitidine hydrochloride prepared by wet granulation technique using hydrophilic polymers like HPMC K100 and HPMC K 15M. It was found that the best formulation RT8 was having the floating lag time 120 seconds and showed 98.4% drug release at the end of 24 hours.
24. **RajiniKanth.P.S *et al,*. (2009)** fabricated floating beads of clarithromycin for prolongation of gastric residence time, leading to an increase in drug bioavailability and sustained action. The beads were prepared by ionotopic gelation method against Helicobacter pylori.
25. **Rajput.G *et al.,* (2009)** reported the floating tablets of Metformin HCl using an effervescent approach for gastro retentive drug delivery system. Floating tablets were prepared using HPMC K100M and HPMC K4M polymers for their gel forming properties. It was concluded that polymer viscosity had major influence on drug release from hydrophilic matrix tablets as well as on floating lag time. As the viscosity increased drug release rate decreased.

26. **Sable.V *et al*., (2010)** formulation and evaluation of floating dosage forms: An overview. Floating dosage forms can be prepared as tablets, capsules, beads by incorporating suitable excipients as well by adding certain gas generating agent gives the buoyancy to the dosage form in gastric fluid.
27. **Sauzet. C *et al.*, (2009**) had formulated different technologies intended for gastro retentive dosage delivery were investigated and patented. The aim of this study was to develop an innovative floating gastro retentive dosage form (GRDF). The developed technology induces a low-density dosage form containing high active pharmaceutical ingredient (API) concentration by using a hydrophobic dusty powder excipient under specific conditions. The new dosage form was obtained by state of the artwet granulation manufacturing process. An apparatus was developed to measure the apparent density of floating tablet. The GRDF was characterized for apparent density, buoyancy, porosity and dissolution using in vitro experimentations.
28. **Sishu, N.Guptha *et al*., (2007):** presented the investigation concerns in the development and evaluation of single unit floating tablets of 5-flurouracil, after oral administration which prolonged the gastric residence time, increased the drug bioavailability and targets the stomach cancer.
29. **Shishu., *et al*., (2009)** urbanized floating beads of 5-Flurouracil for prolongation of gastric residence time, leading to an increase in drug bioavailability and sustained action. The beads were prepared by dispersing 5-FU together with calcium carbonate into a mixture of Na-alginate and HPMC solution and then dripping the dispersion into an acidified solution of calcium carbonate. The

multiple beads was found to reduce tumor incidence in mice 74%, while the conventional tablet reduces tumor incidence in mice only 25%.

30. **Shweta Arora, *et al.*, (2005):** explained that recent developments of FDDS including the physiological and formulation variables affecting gastric retention, approaches to design single-unit and multiple unit floating systems and their classification and formulation aspects in detail.
31. **Thakkar V.T *et al.*, (2008)** evaluated the levofloxacin hemihydrate floating formulations (F1-F9). Selection of optimized batch was done by model dependent approach and novel mathematical approach. F1-F9 batches were prepared by direct compression method using Gelucire 43/01 (hydrophobic) and hydroxypropyl methylcellulose (hydrophilic) polymer in different ratios. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, in vitro buoyancy and in vitro release studies. Various models were used to estimate kinetics of drug release.
32. **Veepabrahma K *et al.* (2009**) discussed floating tablets of Norfloxacin as a model drug for prolongation of gastric residence time, leading to an increase in drug bioavailability. Tablets were prepared by wet granulation technique. The best formulation F4 was selected based on In-vitro characteristics and was used in vivo radiographic studies by incorporating $BaSO_4$
33. **Viral F. Patil *et al.*, (2006):** This describes the development of an intragastric drug delivery system of cefuroxime anxetil. The 32 full factorial design was employed to evaluate contribution of HPMC K4M, HPMC K100 and SLS on drug release from HPMC matrices. It was found that polymer blend and SLS

significantly affect the time required for 50% of drug release, % drug release at 12 hrs.

34. **Vishal G.K *et al.*, (2010)** explained that Floating tablet of Furosemide (FUR) by direct compression technique. Furosemide was chosen as model drug because it is slightly soluble in water and poorly absorb from lower intestine. PEG- 6000 is used as carrier agent for increasing solubility of Furosemide in water. Hydroxypropyl methylcellulose, sodium bicarbonate and carbopol were used as matrixing agent, gas generating agent and floating agent respectively.

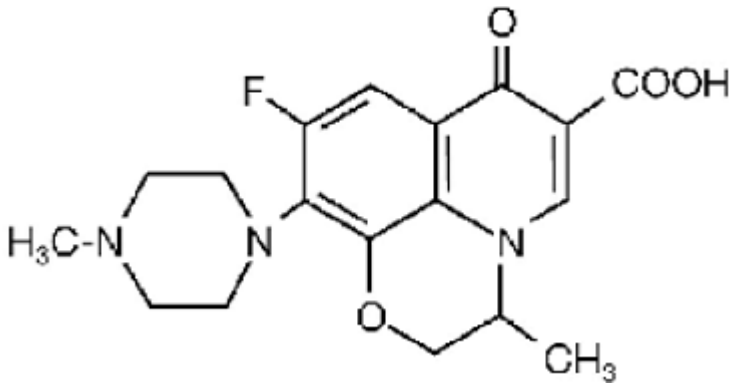
# 2.2. DRUG PROFILE

*(http:// www .google.com; http:// www.rxlist; Indian Pharmacopoeia, 2007)*

## Ofloxacin:

Ofloxacin is a broad spectrum antibiotic that is active against both gram positive and gram negative.

**1. Molecular structure:**




(±)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid

**2. Empirical formula** : $C_{18}H_{20}FN_3O_4$

**3. Mol. Weight** : 361.3 dalton

**4. Category** : Board spectrum antibiotic

**5. CAS Registry No.** : 82419-36-1

**6. Physical state** : Solid off-white to pale yellow crystalline powder

**7. Melting Point** : 250-257 ˚C

**8. Odor** : Odorless

**9. Solubility** : Soluble in glacial acetic acid, slightly soluble in methanol,

methylene chloride and water

**10. Half life** **:** 5-8 hours.

**11. Synonyms** **:** (Zanocin, Travid)

**12. Pharmacology:**

Ofloxacin is a quinolone/fluoroquinolones antibiotic. Ofloxacin is bactericidal and its mode of action depends on blocking of bacterial DNA gyrase, which allows the untwisting required replicating one DNA double helix into two. Notably the drug has 100 times higher affinity for bacterial DNA gyrase than for mammalian. Ofloxacin is a broad-spectrum antibiotic that is active both Gram-positive and Gram-negative bacteria.

**13. Mode of action:**

Ofloxacin is a broad-spectrum antibiotic that is active against both Gram- positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division. The fluroquinolones interfere with DNA replication by inhibiting the enzyme complex called DNA gyrase. This can also affect mammalian cells replication. In particular, some congeners of this drug family display high activity not only against bacterial topoisomerases, but also against eukaryotic topoisomerases and are toxic to cultured mammalian cells and in-vivo tumor models. Although the quinolone is highly toxic to mammalian cells in culture, its mechanism of cytotoxic action is not known, Quinolones induced DNA damage was first reported in 1986.

**14. Pharmacokinetic parameters:**

| **Parameters** | | **Values** |
|---|---|---|
| pKa | : | 6.00 |
| Partition coefficient | : | High |
| Oral absorption | : | 98% |
| Plasma half-life | : | 5-8 hr |
| Volume of distribution | : | 1.8 ±0.3 (liters/kg) |
| Volume protein binding | : | 32% |
| Biotransformation | : | Hepatic |

**15. Adverse Effects:**

Nauesea, vomiting, abdominal pain, diarrhea, headache, insomnia, hallucinations, leucopenia and eoisnophilia, vaginitis, dysgeusia, tendon damage and rupture, anorexia, tremor, photosensitivity, hypersensitivity reactions discontinue if psychiatric, neurological or hypersensitivity reactions discontinue if psychiatric, neurological or hypersensitivity reactions occur. Potentially Fatal, Anaphylaxis, rarely seizures**.**

**16. Therapeutic uses:**

- ✓ Treatment of bacterial infections.
- ✓ Acute bacterial exacerbations of chronic bronchitis.
- ✓ Community-acquired Pneumonia.
- ✓ Uncomlicated skin and skin structure infections.
- ✓ Nongonococcal urethritis and cervicitis.
- ✓ Mixed infections of urethra and cervix.
- ✓ Acute pelvic inflammatory diseases.

- ✓ Uncomplicated cystitis.
- ✓ Complicated urinary tract infections.
- ✓ Acute, Uncomplicated urethral and cervical gonorrhea.

**17. Drug Interactions:**

**Table 2.1:** Drug interactions

| **Drugs** | **Interactions** |
|---|---|
| Acenocoumarol | The quinolone increases the anticoagulant effect |
| Aluminium | Formation of non-absorbable complexes |
| Anisidione | The quinolone increases the anticoagulant effect |
| Bismuth | Formation of non-absorbable complexes |
| Calcium | Formation of non-absorbable complexes |
| Dicumarol | The quinolone increase the anticoagulant effect |
| Dihydroquinidine barbiturate | Increased risk of cardiotoxicity and arrhythmias |
| Foscarnet | Increased risk of convulsions |
| Iron | Formation of non-absorbable complexes |
| Magnesium | Formation of non-absorbable complexes |
| Magnesium oxide | Formation of non-absorbable complexes |
| Quinidine | Increased risk of cardiotoxicity and arrhythmias |
| Quinidine barbiturate | Increased risk of cardiotoxicity and arrhythmias |
| Sucralfate | Formation of non-absorbable complexes |

**18. Dosage administration:**

The usual dose of Ofloxacin tablets is 200mg to 400mg orally 12hrs.

**19. Storage conditions:**

Ofloxacin should be stored at room temperature, protect from sunlight.

**20. Contraindication:**

1. Ofloxacin is now considered to be contraindicated for the treatment of certain sexually transmitted diseases by some experts due to bacterial resistance

2. Ofloxacin is also considered to be contraindicated with

- Pediatric population
- Pregnancy
- Nursing mothers
- Patients with psychiatric illness

# 2.3. POLYMERS PROFILE

## 2.3.1. HYPROMELLOSE (HYDROXYPROPYL METHYLCELLULOSE)

*(Rowe R.C., et al., 2003)*

**A. Nonproprietary Names:**

BP: Hypromellose JP: Hydroxypropylmethylcellulose

PhEur: Hypromellosum USP: Hypromellose

**B. Synonyms:**

*Benecel MHPC*; E464; hydroxypropyl methylcellulose; HPMC; *Methocel*; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; *Metolose*; *Tylopur*.

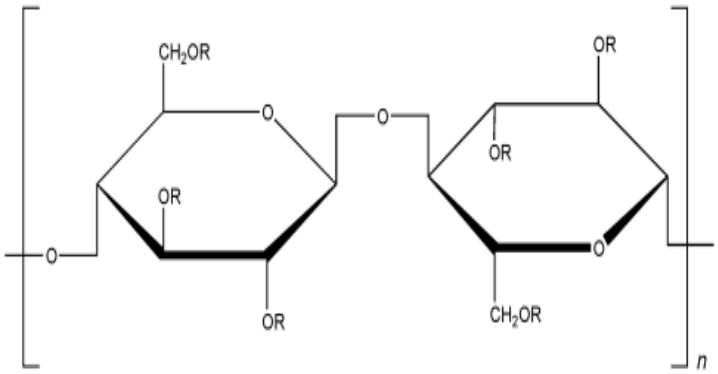
**C. Chemical Name and CAS Registry Number:**

Cellulose hydroxypropyl methyl ether [9004-65-3]

**D. Molecular Weight:**

Molecular weight is approximately 10 000–1 500 000.

**E. Structural Formula:**




Where R is H, $CH_3$, or $CH_3CH$ (OH) $CH_2$

**F. Functional Category:**

Coating agent; film-former; rate-controlling polymer for sustained release; stabilizing agent;suspending agent; tablet binder; viscosity-increasing agent.

**G. Applications in Pharmaceutical Formulation or Technology:**

Hypromellose is widely used in oral, ophthalmic and topical pharmaceutical formulations. In oral products, hypromellose is primarily used as a tablet binder, in film-coating, and as matrix for use in extended-release tablet formulations. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Lower-viscosity grades are used in aqueous film-coating solutions, while higher-viscosity grades are used with organic solvents.

**H. Description:**

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

**I. Typical Properties**

- **Acidity/alkalinity :** pH = 5.5–8.0 for a 1% w/w aqueous solution.
- **Density (bulk) :** 0.341 g/cm3
- **Density (tapped) :** 0.557 g/cm3
- **Density (true) :** 1.326 g/cm3
- **Melting point :** Browns at 190–200°C; chars at 225–230°C.

  Glass transition temperature is 170–180°C.
- **Viscosity (dynamic):** a wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also

be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w.

Typical viscosity values for 2% (w/v) aqueous solutions of Methocel (Dow Chemical Co.). Viscosities measured at 20°C.

**Table 2.2:** Various grades of hypromellose

| Methocel product | USP 28 designation | Nominal viscosity |
|---|---|---|
| Methocel K100 Premium LVEP | 2208 | 100 |
| Methocel K4M Premium | 2208 | 4000 |
| Methocel K15M Premium | 2208 | 15000 |
| Methocel K100M Premium | 2208 | 100000 |
| Methocel E4M Premium | 2910 | 4000 |
| Methocel F50 Premium | 2906 | 50 |
| Methocel E10M Premium CR | 2906 | 10000 |
| Methocel E3 Premium LV | 2906 | 3 |
| Methocel E5 Premium LV | 2906 | 5 |
| Methocel E6 Premium LV | 2906 | 6 |
| Methocel E15 Premium LV | 2906 | 15 |
| Metolose 60SH | 2910 | 50,4000,10000 |
| Metolose 65SH | 2906 | 50,400,1500,4000 |
| Metolose 90SH | 2208 | 100,400,4000,15000 |

- **Solubility:** soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.
- **Moisture content:** hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial moisture content and the temperature and relative humidity of the surrounding air.

**J. Stability and Storage Conditions**

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Increasing temperature reduces the viscosity of solutions. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively.

**K. Incompatibilities**

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts.

**2.3.2. SODIUM BICARBONATE** ***(****Rowe R.C., et al., 2003)*

**A. Nonproprietary Names**

BP: Sodium bicarbonate, JP: Sodium bicarbonate, USP: Sodium bicarbonate

**B. Synonyms**

Baking soda; E500; *Effer-Soda*; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

**C. Chemical Name and CAS Registry Number:**

Carbonic acid monosodium salt [144-55-8]

**D. Molecular Weight:** 84.01

**E. Structural Formula:** $NaHCO_3$

**F. Functional Category:** Alkalizing agent; therapeutic agent.

**G. Description:**

Sodium bicarbonate occurs as an odorless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free-flowing uniform granules.

**H. Typical Properties**

- **Acidity/alkalinity :** pH = 8.3 for a freshly prepared 0.1 M aqueous solution at 25° C.
- **Density (bulk) :** 0.869 g/cm3
- **Density (tapped) :** 1.369 g/ cm3
- **Melting point :** 270° C (with decomposition)
- **Moisture content :** below 80% RH, the moisture content is less than 1% w/w.
- **Solubility:**

Solubility of sodium bicarbonate

**Table 2.3:** Solubility of sodium bicarbonate

| Solvent | Solubility at 20° C unless otherwise stated |
|---|---|
| 3.4 | 4.6 |
| 3.2 | 4.0 |
| 4.1 | 4.4 |

**I. Applications in Pharmaceutical Formulation or Technology**

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and/or tartaric acid; combinations of citric and tartaric acid are often preferred in formulations as citric acid alone produces a sticky mixture that is difficult to granulate, while if tartaric acid is used alone, granules lose firmness.

**J. Uses of sodium bicarbonate**

| **Use** | **Concentration (%)** |
|---|---|
| Buffer in tablets | 10–40 |
| Effervescent tablets | 25–50 |

**K. Stability and Storage Conditions**

When heated to about 50° C, sodium bicarbonate begins to dissociate into carbon dioxide, sodium carbonate, and water; on heating to 250–300°C

**2.3.3. MAGNESIUM STEARATE** ***(****Rowe R.C., et al., 2003)*

**A. Nonproprietary Names:**

BP: Magnesium stearate, JP: Magensium stearate, USP: Magnesium stearate

**B. Synonyms:** Metallic stearate, magnesium salt.

**C. Chemical Name**: Octadecanoic acid, magnesium salt

**D. Empirical Formula:** $C_{36}H_{70}MgO_4$

**E. Molecular Weight:** 591.34

**F. Structural Formula:** $[CH3\ (CH_2)_{16}COO]_2\ Mg$

**G. Functional Category:** Tablet and capsule lubricant.

**H. Description:**

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.

**I. Typical Properties:**

Density (bulk): 0.159 g/cm$^3$

Density (tapped): 0.286 g/cm$^3$

**J. Solubility:**

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%)

**K. Applications in Pharmaceutical Formulation**:

Magnesium stearate is used in foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 – 5.0%.

**L. Stability and Storage Conditions:**

Magnesium stearate is stored in a well-closed container in a cool, dry place.

### 2.3.4. LACTOSE

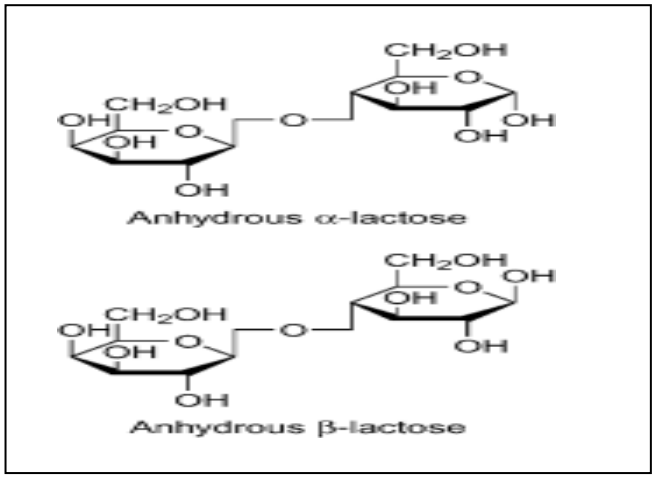
**A. Synonyms:** Anhydrous Lactose NF 60M, lactosum, milk sugar.

**B. Chemical Name:** O-β-D-galactopyranosyl-(1→4)-β-D-glucopyranose .

**C. CAS Registry Number:** [63-42-3]

**D. Molecular Weight:** 342.30.

**E. Structural Formula:**




**F. Functional Category:**

Binding agent; directly compressible tableting excipient; lyophilization aid; tablet and capsule filler.

**G. Applications in Pharmaceutical Formulation or Technology**

Anhydrous lactose is widely used in direct compression tableting applications and as a tablet and capsule filler and binder. Anhydrous lactose can be used with moisture-sensitive drugs due to its low moisture content.

**H. Angle of repose:** 39° for Pharmatose DCL 21 and 38° for Super-Tab Anhydrous.

**I. Density (true):** 1.589 g/cm3 for anhydrous β-lactose; 1.567 g/cm3 for Super-Tab

**Density (bulk):** 0.68 g/cm3 for Pharmatose DCL 21; 0.67 g/cm3 for Pharmatose DCL 22; 0.65 g/cm3 for Super-Tab Anhydrous.

**Density (tapped):** 0.88 g/cm3 for Pharmatose DCL 21; 0.79 g/cm3 for Pharmatose DCL 22; 0.87 g/cm3 for Super-Tab Anhydrous.

**J. Melting point:**

- 223.0°C for anhydrous α-lactose;

- 252.2°C for anhydrous β-lactose;
- 232.0°C (typical) for commercial anhydrous lactose.

**K. Moisture content**: Anhydrous lactose normally contains upto 0.1% w/w water. Lactose monohydrate contains approximately 5% water of crystallization.

**L. Stability and storage**: saturated solutions of β lactose may precipitate crystals of lactose on standing. It should be stored in a well closed container in a cool, dry place.

### 2.3.5. SODIUM LAURYL SULFATE *(Rowe R.C., et al., 2003)*

**A. Nonproprietary Names:**

BP: Sodium lauryl sulfate, USPNF: Sodium lauryl sulphate, PhEur: Natrii lauryl sulfas

**B. Synonyms:** Dodecyl sodium sulfate, Elfan240, Sodium mono dodecyl sulfate.

**C. Chemical Name**: Sulphuric acid monododecyl ester sodium salt

**D. Empirical Formula:** $C_{12}H_{25}NaO_4S$.

**E. Molecular Weight:** 288.38.

**G. Functional Category:** Anionic surfactant, detergent, emulsifying agent, tablet lubricant.

**H. Description:**

It consists of white or cream to pale yellow colored crystals, flakes or powder having smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

**I. Typical Properties:** Density: 1.07 $g/cm^3$

**J. Solubility:** Practically insoluble in ethanol, chloroform; freely soluble in water.

**K. Applications in Pharmaceutical Formulation**:

SLS is used as surfactant lubricant.

**L. Stability and Storage Conditions:**

It is stable under normal storage conditions. However in solution under extreme conditions, i.e; $P^H$ 2.5 (or) below it may undergoes hydrolysis to lauryl alcohol and sodium bisulphate.

The bulk material should be a stored in a well closed container away from strong oxidizing agents in a cool, dry place.

# AIM & OBJECTIVES

# 3. AIM AND OBJECTIVES

Anti microbial agents are orally administered to produce a systemic effect, but this application induces some side effects like hypersensitivity, gastrointestinal intolerance, development of bacterial resistance. Furthermore, it is reported that this kind of administration does not guarantee an adequate concentration at the action site because the active product is not retained locally for a sufficient period of time. A solution to these problems could be the local administration of the drug formulated in a controlled release delivery system was developed for site specific delivery of ofloxacin.

Ofloxacin is a synthetic chemotherapeutic antibiotic of fluroquinolones drug class considered to be a second generation fluroquinolones. Ofloxacin is the broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative. Ofloxacin is more potent against gram positive organism and certain anaerobes when compared with other fluroquinolone antibiotics.

Floating sustained release delivery systems for oral dosing are effective in achieving optimal therapy with drugs that have a narrow therapeutic range of blood concentration which eliminate rapidly. One of the methods of fabricating sustained release formulations in incorporation of the drug in the floating matrix containing a hydrophilic rate controlling polymer. The FDDS is able to prolong the retention time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug. These are matrix type of systems prepared with the help of swellable polymer and various effervescent agents, e.g. sodium bicarbonate and citric acid.

But, till now not a single attempt has been made to develop a floating tablets of ofloxacin which release the drug slowly over an extended period of time with prolonged gastric retention.

Hence, the present work involves use of gastric floating drug delivery system for ofloxacin which is primarily absorbed in the stomach and upper intestine segments. This will ensure minimum fluctuations in the plasma drug concentration and reduced dosing frequency which will result into improved patient compliance.

# PLAN OF WORK

# 4. PLAN OF WORK

- **Literature survey**
- **Materials and equipments**
- **Preformulation studies**
  - **Characterization of Drug**
    - Colour and Appearence
    - Melting Point Determination
    - Solubility Study
  - **Identification of Drug**
    - FTIR
    - UV Spectral analysis
    - Loss on drying
  - **Drug - Polymers Compatibility Studies**
    - Differential Scanning Calorimetry (DSC) Analysis
  - **Preparation and Evaluation of Powder blends**
    - Angle of repose
    - Bulk density and tapped density
    - Carr's Compressibility Index
    - Hausner's ratio
- **Formulation of Floating Tablets**
  - **Evaluation of Tablets**
    - **Physico-Chemical Properties of Tablets**

- Appearance
- Size and Thickness
- Hardness
- Friability
- Weight variation
- Drug content

- **Swelling Index of Tablets**
- ***In vitro* Buoyancy Studies**
- ***In vitro* Drug Release Studies**
- **Kinetics of *In vitro* drug release**
- **Stability Studies**

- **Results and Discussion**
- **Summary and Conclusion**
- **Future Prospects**
- **Bibliography**

# MATERIALS & EQUIPMENTS

# 5. MATERIALS AND EQUIPMENTS

## 5.1. LIST OF MATERIALS USED WITH SOURCES

**Table 5.1:** List of Materials and their Suppliers

| Sl. No. | Name of Material | Supplied by |
|---|---|---|
| 1 | Ofloxacin | Goodman pharmaceuticals, Pondicherry. |
| 2 | HPMC K15 | Loba chemie,Mumbai. |
| 3 | HPMC K100 | Cipla Laboratories, Mumbai. |
| 4 | Sodium bicarbonate | Cipla Laboratories, Mumbai. |
| 5 | Sodium lauryl sulfate | Cipla Laboratories, Mumbai. |
| 6 | Magnesium stearate | Loba Chemicals, Mumbai |
| 7 | Lactose | Loba Chemicals, Mumbai |

## 5.2. LIST OF USED EQUIPMENTS WITH MAKE/MODEL:

**Table 5.2:** List of equipments with their make and model

| Sl. No. | Name of the equipment | Make |
|---|---|---|
| 1 | Electronic balance | Shimadzu, Japan |
| 2 | UV-Visible spectrophotometer | Shimadzu, Japan |
| 3 | 16 Stations rotary tablet compression machine | Cadmach, Ahmedabad, India |
| 4 | Hardness tester | Monsanto |
| 5 | Roche friability tester | Veego scientifics, Mumbai |
| 6 | FTIR Spectrophotometer | Perkin elmer-Pharmaspec-1 |
| 7 | Dissolution test apparatus | Veego scientifics, Mumbai |
| 8 | Digital pH meter | Elico scientifics, Mumbai |
| 9 | Hot air oven | Prescision scientific co., Chennai |
| 10 | Vernier calipers | Indolabs, Chennai |
| 11 | Humidity chamber | Labtech, Ambala |
| 12 | Tap density apparatus | Indolabs, Chennai |
| 13 | Melting point test apparatus | Prescision scientific co., Chennai |
| 14 | Standard sieve | Jayant scientific, India |

# PRE-FORMULATION STUDIES

# 6. PRE-FORMULATION STUDIES

## 6.1. CHARACTERIZATION OF DRUG:

### 6.1.1. Colour and Appearance: *(Indian Pharmacopoeia, 2007)*

The sample was observed visually.

### 6.1.2. Melting Point: *(Indian pharmacopeia,2007)*

Melting point of drug was determined by Melting point test apparatus.

### 6.1.3. Solubility Study: *(Indian Pharmacopoeia, 2007)*

Solubility study was carried out as per the I.P.2007.In this maximum amount of solvent required to dissolve the solute was determined.

### 6.1.4. Identification of drug:

#### 6.1.4.1. Identification of drug by FTIR:

FTIR study was carried out to identify drug. Infrared spectrum of Ofloxcain was determined on Fourier transform Infrared Spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by using Parkin elmer-Pharmaspec-1 FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum

### 6.1.4 Spectral Analysis of Ofloxacin: (Bhusari KP; 2009)

#### 6.1.4.1 UV Spectral Analysis of Ofloxacin:

##### 6.1.4.1.1. UV Spectral Analysis of Ofloxacin in 0.5N acetic acid:

**6.1.4.1.1.1. Determination of absorption maximum in 0.5N acetic acid:**

Stock solution of Ofloxacin (1000 µg/ml) was prepared by dissolving 50 mg of Ofloxacin in 50 ml of 0.5 N Acetic acid. Dilutions of ( 2-10 µg/ml) were performed. The solution was scanned in range of wavelength 210-400 nm, for determining absorption maxima ($\lambda_{max}$) of Ofloxacin by drug by using Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer**.**

**6.1.4.1.1.2. Preparation of Standard Curve of Ofloxacin:**

Stock solution of Ofloxacin (1000 µg/ml) was prepared by dissolving 50ml of drug of 0.5N Acetic acid. The dilutions of 2-10 µg/ml were prepared from stock solution. The UV absorbances of these solutions were determined spectrometrically at $\lambda_{max}$ 294 nm using UV-VISIBLE Spectrophotometer.

❖ **Assay of Ofloxacin:**

Accurately weighed 50 mg of Ofloxacin was dissolved in little quantity of 0.5 N acetic acid and volume was adjusted to 50 ml with the same to prepare standard solution having concentration of 1000 µg/ml and the volume was adjusted with 0.5 N acetic acid to get a concentration of 100 µg/ml. From this stock solution, 0.5 ml was pipette out and transferred to 10 ml volumetric flask and final volume was adjusted with 0.5N acetic acid. Absorbance values of these solutions were measured against blank at 294 nm using UV-Visible spectrophotometer. The percentage purity of drug was calculated by using calibration graph method.

**6.1.4.1.2.2. . UV Spectral Analysis of Ofloxacin in 0.1 N HCl:**

**6.1.4.1.2.2.1. Determination of absorption maximum in 0.1 N HCl:**

Stock solution of Ofloxacin (1000 µg/ml) was prepared by dissolving 50 mg of Ofloxacin in 50 ml of 0.1 N HCl. Dilutions of ( 3-15 µg/ml) were performed. The solution was scanned in range of wavelength 210-400 nm, for determining absorption maxima ($\lambda_{max}$) of Ofloxacin by drug by using Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer**.**

**6.1.4.1.2.2.2. Preparation of Standard Curve of Ofloxacin:**

Stock solution of Ofloxacin (1000 µg/ml) was prepared by dissolving 50ml of drug of 0.1 N HCl. The dilutions of 3-15 µg/ml were prepared from stock solution. The UV absorbances of these solutions were determined spectrometrically at $\lambda_{max}$ 293.2 nm using UV-VISIBLE Spectrophotometer.

.

**6.1.5. Loss on drying:** *(Indian Pharmacopoeia, 2007)*

Loss on drying is the loss of weight expressed as percentage w/w resulting from volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.

$$\textbf{Loss on drying} = \frac{\textbf{Initial weight of substance} - \textbf{Final weight of substance}}{\textbf{Initial weight of substance}} \times 100$$

## 6.2. DRUG - POLYMERS COMPATABILITY STUDIES :

Drug polymers studies holds great importance in designing a formulation In drug formulation it is essential to evaluate the possible interactions between the active principle and the polymers, as the choice of the polymers should be performed in relation to the drug delivery, to their compatibility with the same drug and to the stability of the final product.

### 6.2.1. Differential Scanning Calorimetry Study (DSC): *(Jain N. K., 2008)*

Ofloxacin powder was mixed with various polymers in the ratio of 1:1. The mixture of drug with polymers to maximize the like hood of obscuring an interaction. Mixture should be examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate ($10^0$C/minute) on DSC. Over a temperature range, which will encompass any thermal changes due to the mixture of drug with polymers. Thermograms of pure drug are used as a reference.

Appearance or disappearance of one or more peaks in thermograms of drug with polymer are considered as a indication of interaction.

## 6.3 PREPARATION AND EVALUATION OF POWDER BLENDS

### 6.3.1 PREPARATION OF POWDER BLENDS:

All ingredients were weighed and passed through mesh #40 seperately. The drug and polymer were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 20 min. Finally the blend is passed through mesh # 20 and used for evaluation of flow characteristics.

### 6.3.2 EVALUATION OF MICROMERITIC PROPERTIES OF POWDERS

*(Aulton M.E., 2007; Sinko P. J., 2009; Ansel S. C.,)*

**6.3.2.1 Angle of Repose:**

The angle of repose was determined by the funnel method. The accurately weighed (10 gms) powder was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of powder. The powder was allowed to flow through the funnel freely onto a clean surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\tan \theta = h/r$$

Where h is the height of powder cone and r is the radius of the powder cone. Relationship between angle of repose (θ) and flowability is shown in the Table 6.1.

**Table** 6.1: Relationship between Angle of Repose (θ) and Flowability

| Sl. No. | Angle of repose(θ) | Flowability |
|---|---|---|
| 1 | <20 | Excellent |
| 2 | 20 – 30 | Good |
| 3 | 30 – 35 | Passable |
| 4 | >40 | Very poor |

**6.3.2.2. Bulk Density and Tapped Bulk Density:**

An accurately weighed (10 gms) powder from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the powder was measured which give bulk volume. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. Both Bulk Density (BD) and Tapped Bulk Density (TBD) of powder were determined using the following formulae.

**BD = Weight of the powder/Volume of the powder**

**TBD = Weight of the powder/Tapped volume of the powder**

**6.3.2.3. Carr's Compressibility Index:**

The compressibility index of the powder was determined using following Carr's compressibility index formula.

**Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100**

Relationship between % compressibility and flowability is shown in the Table 6.2

**Table 6.2: Relationship between % Compressibility and Flowability**

| Sl. No. | % Comressibility | Flowability |
|---|---|---|
| 1 | 5-15 | Excellent |
| 2 | 12-16 | Good |
| 3 | 18-21 | Fair Passable |
| 4 | 23-35 | Poor |
| 5 | 33-38 | Very poor |
| 6 | >40 | Very very poor |

**6.3.2.4. Hausner's ratio:**

Hausner's ratio is the ratio between tapped density and bulk density.

Hausner's ratio less than 1.25 indicates good flow properties while Hausner's ratio greater than 1.25 shows poor flow of powder.

**Table 6.3: Relationship between Hausner's ratio and Flowability**

| Sl. No. | Hausner's ratio | Flow Property |
|---|---|---|
| 1 | 0.0 - 1.25 | Free flow |
| 2 | 1.25 - 1.6 | Cohesive flow |

# FORMULATION OF TABLETS

# 7. FORMULATION OF FLOATING TABLETS

*(Vital F. Patel et al, 2006)*

The formulation of Ofloxacin tablets was calculated by using $3^2$ full factorial design was used in development of dosage form. In this design, 2 factors were evaluated each at three levels and experimental trials were performed using all possible nine combinations. In this present investigation, the ratio of HPMC K15:HPMC K100 (X1) and content of sodium laurel sulfate (X2) were selected as independent variables.

The experimental design with corresponding formulations is outlined in table . Content of polymer blend was 15% of the total tablet weight. Blends of HPMC K15 and HPMC K100 were evaluated at 85:15, 75:25 and 65:35, while content of SLS was evaluated at 0%, 1%, 2% of the total tablet weight.

A statistical model incorporating interactive and polynomial terms was used to evaluate the response.

$$Y=b0 + b1X1 + b2X2 + b12X1X2 + b11X1X1 + b22X2X2.$$

Where Y= Dependent variable

b0= arithmetic mean response of 9 runs,

b1= estimated coefficient factor, $X_i$

The main effect (X1:X2) represents the average result of changing one factor at a time from its low to high value. The interaction term (X1X2,X2X2) are included to investigate non linearity.

Independent variables and their selected levels for floating tablet formulation

**Table 7.1:** Ratio's of polymer used in the formulation

| Sl.No | Code values | Actual values in mg | |
|---|---|---|---|
| | | HPMC K15:HPMC K100 | SLS |
| 1 | -1 | 85:15 | 0% |
| 2 | 0 | 75:25 | 1% |
| 3 | 1 | 65:35 | 2% |

## 7.1 FORMULATION OF OFLOXACIN TABLET USING $3^2$ FULL FACTORIAL DESIGNS

**Table 7.2:** Formulation of ofloxacin using $3^2$ full factorial design

| Sl.NO | BATCH CODE | Variable level in Code | |
|---|---|---|---|
| | | X1 | X2 |
| 1 | F1 | +1 | +1 |
| 2 | F2 | +1 | 0 |
| 3 | F3 | +1 | -1 |
| 4 | F4 | 0 | +1 |
| 5 | F5 | 0 | 0 |
| 6 | F6 | 0 | -1 |
| 7 | F7 | -1 | +1 |
| 8 | F8 | -1 | 0 |
| 9 | F9 | -1 | -1 |

**Table 7.3: Composition of floating Tablets of Ofloxacin:**

| Sl. No. | Ingredients (mg/tablet) | Formulations Code | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** |
| 1 | **Ofloxacin** | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 | 400 |
| 2 | **HPMCK15**<br>**HPMCK100** | 58.5<br>31.5 | 58.5<br>31.5 | 58.5<br>31.5 | 67.5<br>22.5 | 67.5<br>22.5 | 67.5<br>22.5 | 76.5<br>13.5 | 76.5<br>13.5 | 76.5<br>13.5 |
| 3 | **Sodium lauryl sulfate** | 12 | 6 | 0 | 12 | 6 | 0 | 12 | 6 | 0 |
| 4 | **Sodium bicarbonate (10%)** | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| 5 | **Magnesium stearate(1%)** | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| 6 | **Lactose** | 32 | 38 | 44 | 32 | 38 | 44 | 32 | 38 | 44 |
| 7 | **Total** | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 | 600 |

## 7.2 COMPRESSION OF POWDER BLENDS INTO TABLETS

**(***Dhirendra K., et al., 2010)*

After evaluation of powder blend, the floating tablets were prepared by direct compression method using (9 mm diameter, round flat faced punches) multiple punch tablet compression machine (Cadmach Machinery Ltd., Ahmedabad, India). Each tablet contained 400 mg of Ofloxacin; the batch size for each formulation was 100 tablets.

# EVALUATION OF TABLETS

# 8. EVALUATION OF TABLETS

- **Evaluation of Tablets:**
  - **Physicochemical Properties of Tablets**
    - Appearance
    - Thickness
    - Hardness
    - Friability
    - Weight variation
    - Drug content
  - **Swelling Index of Tablets**
  - ***In vitro* Buoyancy Studies**
  - ***In vitro* Drug Release**
  - **Kinetics of *in vitro* Drug Release**
  - **Stability Studies**

**8.1. Physicochemical Properties of Tablets:**

**8.1.1. Appearance:** *(Lachman L., 1990)*

The tablets were visually observed for any capping, chipping and lamination.

**8.1.2. Size and Thickness:**

The size and thickness of tablet can vary with no change in weight due to difference in Density of granulation, the pressure applied to the tablets and speed of the tablet compression machine. The thickness of the tablets was determined using a Vernier caliper. Three tablets from each type of formulation were used and average values were calculated.

**8.1.3. Hardness:**

There is a certain requirement of hardness in tablets so as to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. Hardness tester (Monsanto tester) was used to measure hardness of tablets. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be taken as a zero $kg/cm^2$. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in $kg/cm^2$.

**8.1.4. Friability:**

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for four minutes, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as follows,

**% Friability = (Initial weight - Final weight / Initial weight) x 100.**

**8.1.5. Weight Variation:** *(Indian Pharmacopoeia, 2007)*

The weight variation test is done by taking 20 tablets randomly and they were weighed individually. The composite weight divided by 20, provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by % deviation allowed and none should deviate by more than twice it's percentage.

**Table 8.1: Specifications of % Weight Variation Allowed in Tablets as per Indian Pharmacopoeia**

| Average Weight of Tablet | % Deviation allowed |
|---|---|
| 80 mg or less | 10 |
| More than 80 mg but less that 250 mg | 7.5 |
| 250 mg or more | 5 |

***8.1.6.*** **Drug Content :** *(Hanna Hopkala, 2000)*

Twenty tablets were weighed and finely powdered. An accurately weighed quantity of powder equivalent to 50 mg of Ofloxacin was taken in 50 ml volumetric flask and dissolved in 25 ml of 0.5 N Acetic acid; it was further diluted up to the mark with same solvent. The solutions were then filtered and filterate gets diluted to get 5 µg/ml concentration of Ofloxacin. The solution was then read at 294 nm by using UV-VISIBLE spectrophotometer.

**8.2. Swelling Index of Tablets:** *(NG Raghavendra Rao,2011)*

The extent of swelling was measured in terms of percentage weight gain by the tablet. The swelling behaviour of formulation F1-F9 was studied. One tablet from each formulation was kept in a petritdish containing 0.1N HCl. The tablet was withdrawn in time intervals, soaked with tissue paper, and weighed. Weights of the tablet were noted and the process was continued till the end 12 hrs. Percentage weight gain by the tablet was calculated by formula.

$$\text{Swelling Index} = \frac{\text{Weight of swollen tablet - Initial weight of tablet}}{\text{Initial weight of tablet}}$$

**8.3. *In vitro* Buoyancy Studies:** *(NG Raghavendra Rao et al,2011)*

The time taken for tablet to emerge on the surface of the medium is called the floating lag time or buoyancy lag time and duration of time the dosage form constantly remains on the surface of the medium is called total floating time. The buoyancy of the tablets was performed by using 0.1 N HCl. The time of duration of floatation was observed visually.

**8.4. *In vitro* Drug release studies of Tablets:** (*Indian Pharmacopoeia,2007)*

The release rate of Ofloxacin from floating tablets was determined using USP Dissolution Testing Apparatus type-II (paddle method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed using 900 ml of 0.1N HCl, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and diluted to a suitable

concentration with 0.1N HCl. Absorbance of these solutions was measured at 293.2 nm using a Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. For each formulation, the experiments were carried out in triplicate. The release data were calculated by using PCP disso V3 software.

**8.5. Kinetics of *In vitro* Drug Release:** *(Brahmankar D.M., 2009)*

To analyze the mechanism of drug release from the tablets the *In-vitro* drug release, data were fitted to kinetic models such as zero order, first order, Higuchi and Korsmeyer-Peppas.

- **Zero order:** $C = K_0 t$

$K_0$ - zero-order rate constant expressed in units of concentration/time, t - time in hrs.

- **First order:** $LogC = LogC_0 - Kt / 2.303$

Where $C_0$ - is the initial concentration of drug, $K$ - first order constant, $t$ - time in hrs.

- **Higuchi :** $Qt = Kt^{1/2}$

Where $Q_t$ - amount of the release drug in time t, $K$- kinetic constant, t- time in hrs.

- **Korsmeyer Peppas:** $Mt / M\infty = Kt\, n$

Where $M_t$ - represents amount of the released drug at time t,

$M_\infty$- is the overall amount of the drug (whole dose) released after 12 hrs

K- is the diffusional characteristic of drug/ polymer system constant

n- is a diffusional exponent that characterizes the mechanism of release of drug.

**8.6. STABILITY STUDIES***:* *(Anand Patel,2009)*

To assess the drug and formulation stability, stability studies were done according to International Conference on Harmonization and World Health Organisation guidelines. The tablets were stored at 40ºC/75% relative humidity in closed high-density

polyethylene bottles for 3 months. Tablets were analyzed at specific time intervals for hardness, drug content, *invitro* buoyancy studies, *invitro* drug release studies.

# RESULTS
# &
# DISCUSSION

# 9. RESULTS AND DISCUSSION

**CHARACTERIZATION OF DRUG:**

### 9.1.1. Colour and Appearance:

The drug (Ofloxacin) colour is "Off-white to pale yellow" as same as the reported reference.

### 9.1.2. Melting Point:

The Melting point of Ofloxacin was found to be 256.056 ± 0.040. The reported melting point of Ofloxacin is 250-257$^0$C. Hence, observed values are complies with USP.

### 9.1.3. Solubility Study:

The Solubility of Ofloxacin in different solvents is given below:

**Table 9.1:** Solubility of Ofloxacin in Different Solvents

| Sl. No. | Solvent | Parts of solvent required per part of solute | Inference |
|---|---|---|---|
| 1 | Acetic acid | 10 | Soluble. |
| 2 | Water | 460 | Slightly soluble. |
| 3 | 0.1 N HCl | 28 | Soluble. |

### 9.1.4. IDENTIFICATION OF DRUG:

Identification of drug was performed by FTIR spectroscopic method

### 9.1.4.1. Fourier Transform Infra-Red Spectroscopy (FTIR):

The IR spectrum of Ofloxacin is shown in figure 9.1. The Interpretation of IR frequencies are show in Table 9.2.

**FTIR spectroscopy:**

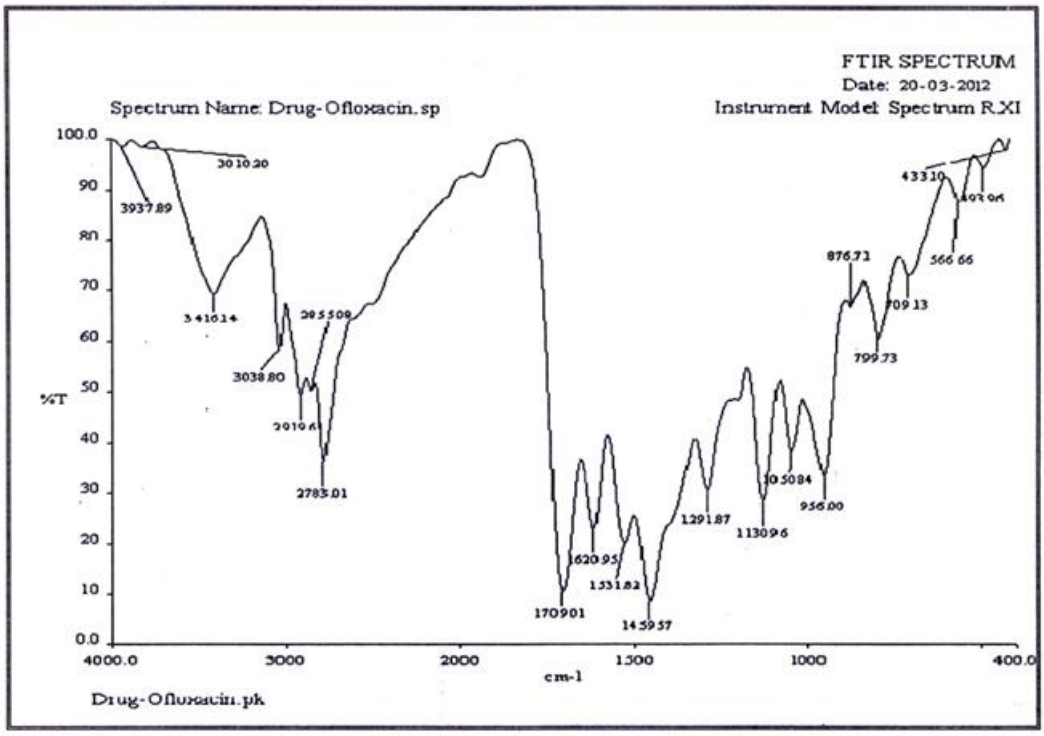



**Fig 9.1:** FTIR of ofloxacin

### Interpretation of FTIR Spectrum:

Table 9.2 shows the peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of Ofloxacin. Hence, the sample was confirmed as Ofloxacin.

**Table 9.2:** Characteristic Frequencies in FTIR Spectrum of Ofloxacin

| Functional groups | Wave No. ($cm^{-1)}$ |
|---|---|
| C-H out of plane bending | 799 |
| C-O-C stretching ether group | 1050 |
| C-F stretching | 1130 |
| C-O stretching COOH | 1291 |
| C-C stretching | 1459 |
| C=O aromatic stretching | 1531 |
| C=O stretching ketones | 1620 |

### 9.1.5. SPECTROSCOPIC STUDIES:

#### 9.1.5.1. UV Spectroscopy:

##### 9.1.5.1.1. Determination of λmax and Preparation of Calibration Curve of Ofloxacin by using 0.5 N Acetic acid:

UV absorption spectrum of Ofloxacin in 0.5 N Acetic acid shows λmax at 294nm. Absorbance obtained for various concentrations of Ofloxacin in 0.5 N Acetic acid are given in Table 9.3. The graph of absorbance concentration for Ofloxacin was found to be linear in the concentration range of 2-10 µg /ml. The drug obeys Beer-Lambert's law in the range of 2-10 µg /ml.

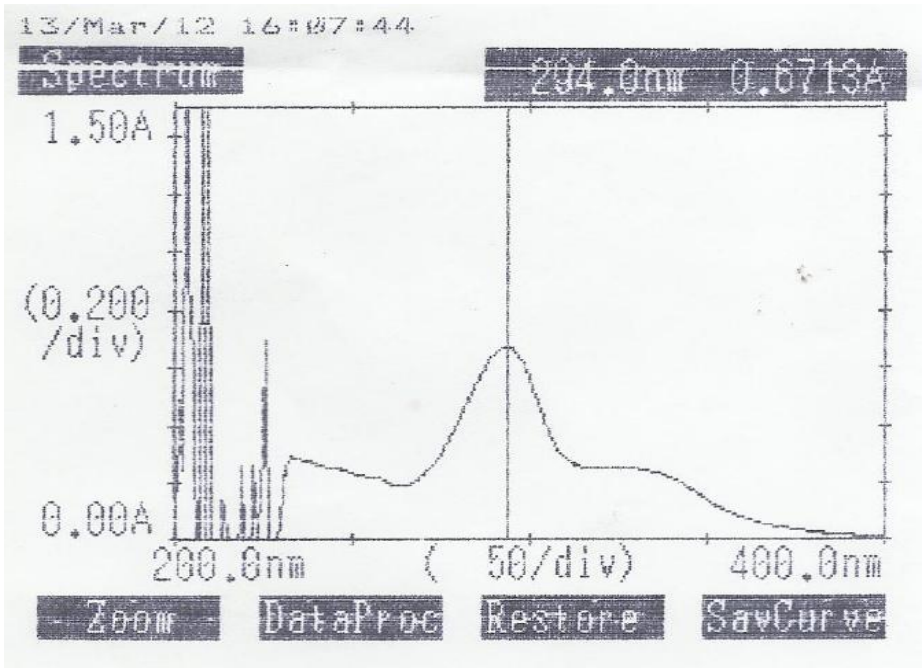



**Fig. 9.2:** Absorption maximum of Ofloxacin in 0.5N Acetic acid

**Table 9.3:** Concentration and Absorbance data for Calibration Curve of Ofloxacin in 0.5 N Acetic acid

| Sl. No. | Concentrations(µg/ml) | Absorbance at 294nm. |
|---|---|---|
| 1 | 2 | 0.191 |
| 2 | 4 | 0.360 |
| 3 | 6 | 0.540 |
| 4 | 8 | 0.711 |
| 5 | 10 | 0.870 |

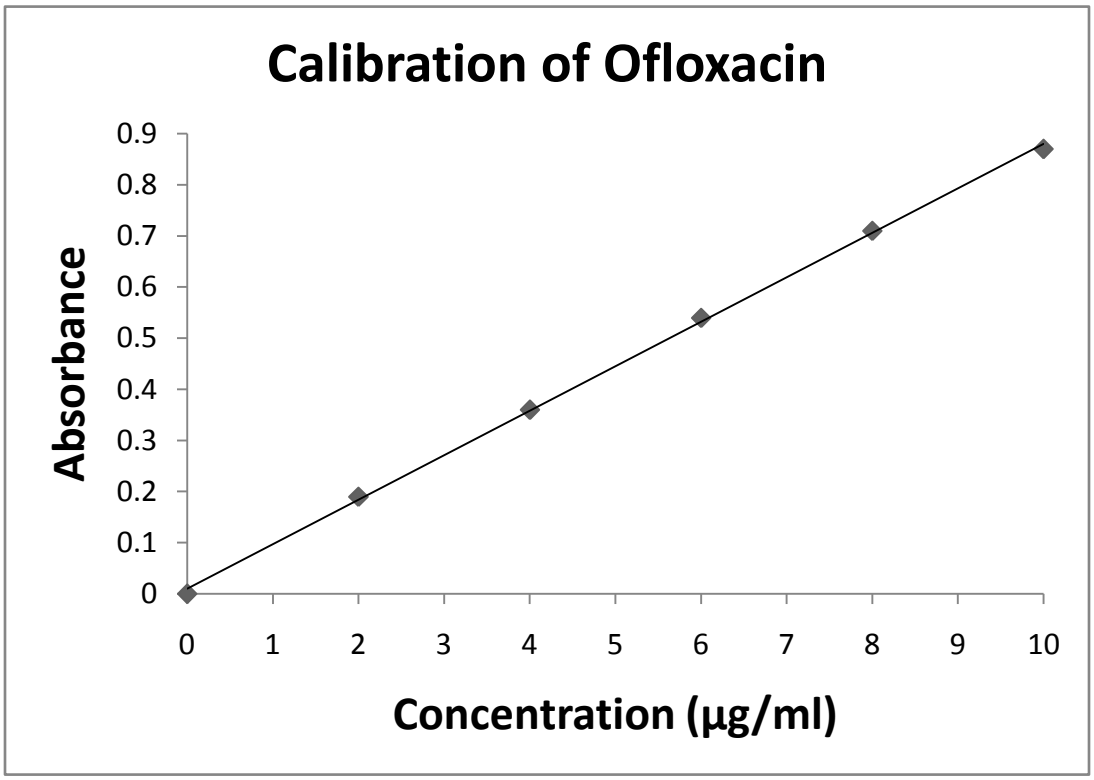



**Fig.9.3** Calibration curve of Ofloxacin in 0.5 N acetic acid

The values of Correlation coefficient (R), Slope, Intercept obtained from the calibration curve are given in the Table 9.4.

**Table 9.4:** Data for Calibration Curve parameters of Ofloxacin in 0.5 N Acetic acid

| Sl. No. | Parameters | Values |
|---|---|---|
| 1 | Slope | 0.0850 |
| 2 | Intercept | 0.0210 |
| 3 | Correlation coefficient (R) | 0.9998 |

**9.1.5.1.2. Assay of Ofloxacin:**

**Table 9.5:** Assay of Ofloxacin

| Sl. No | Percentage Purity | Average Percentage purity(%) |
|---|---|---|
| 1 | 99.86 | 100.38±0.714 |
| 2 | 100.10 | |
| 3 | 101.20 | |

The official percentage purity of Ofloxacin is not less than 98.5% and not more than 101.5%. So it can be declared as pure drug. The percentage purity of raw material Ofloxacin was found to be 100.38±0.714. Hence, the sample was concluded as pure

**9.1.5.1.3. Determination of λmax and Preparation of Calibration Curve of Ofloxacin by using 0.1N HCl:**

UV absorption spectrum of Ofloxacin in 0.1N HCl shows λmax at 293.2 nm. Absorbance obtained for various concentrations of Ofloxacin in 0.1N HCl are given in Table 9.6. The graph of absorbance versus concentration for Ofloxacin was found to be linear in the concentration range of 3-15 µg /ml. The drug obeys Beer- Lambert's law in the range of 3-15 µg /ml.

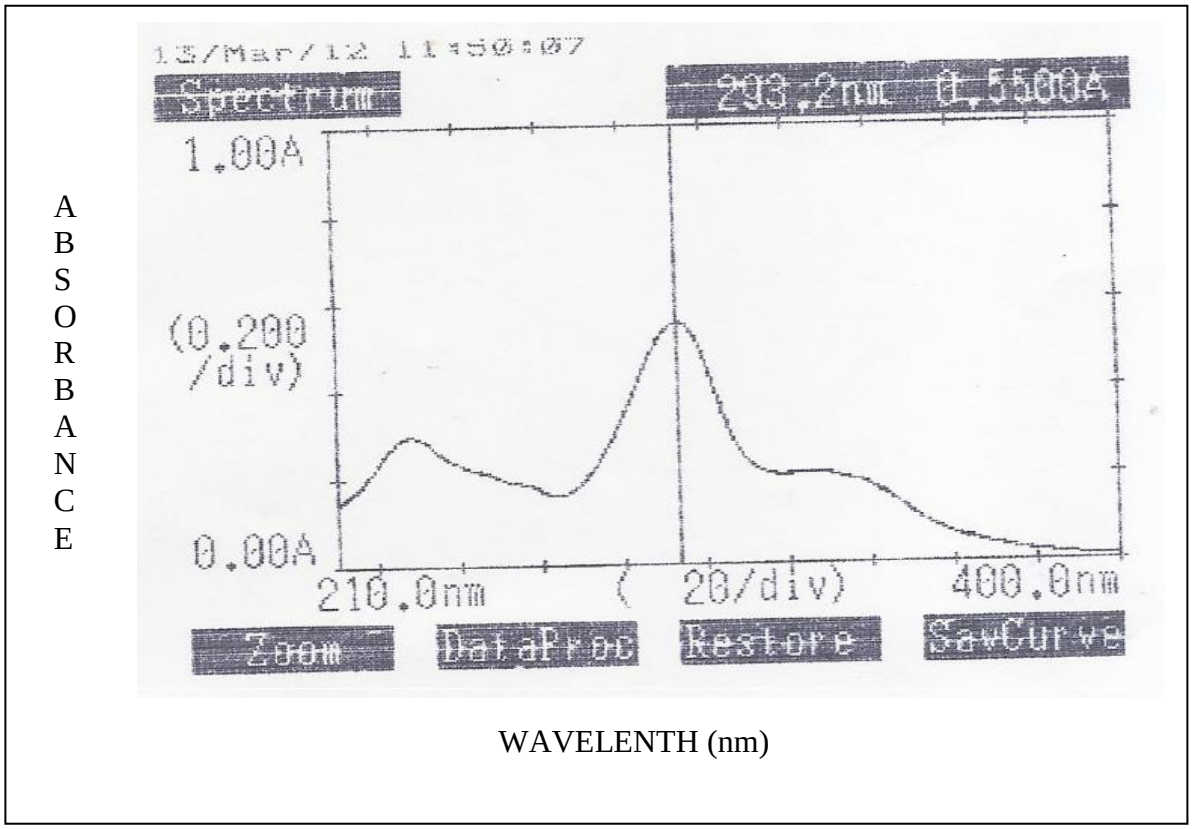



**Fig. 9.4:** Absorption maxima of Ofloxacin in 0.1N HCl

**Table 9.6:** Concentration and Absorbance data for Calibration Curve of Ofloxacin in 0.1N HCl:

| Sl. No. | Concentrations (µg/ml) | Absorbance at 293.2nm |
|---|---|---|
| 1 | 3 | 0.182 |
| 2 | 6 | 0.355 |
| 3 | 9 | 0.529 |
| 4 | 12 | 0.701 |
| 5 | 15 | 0.875 |

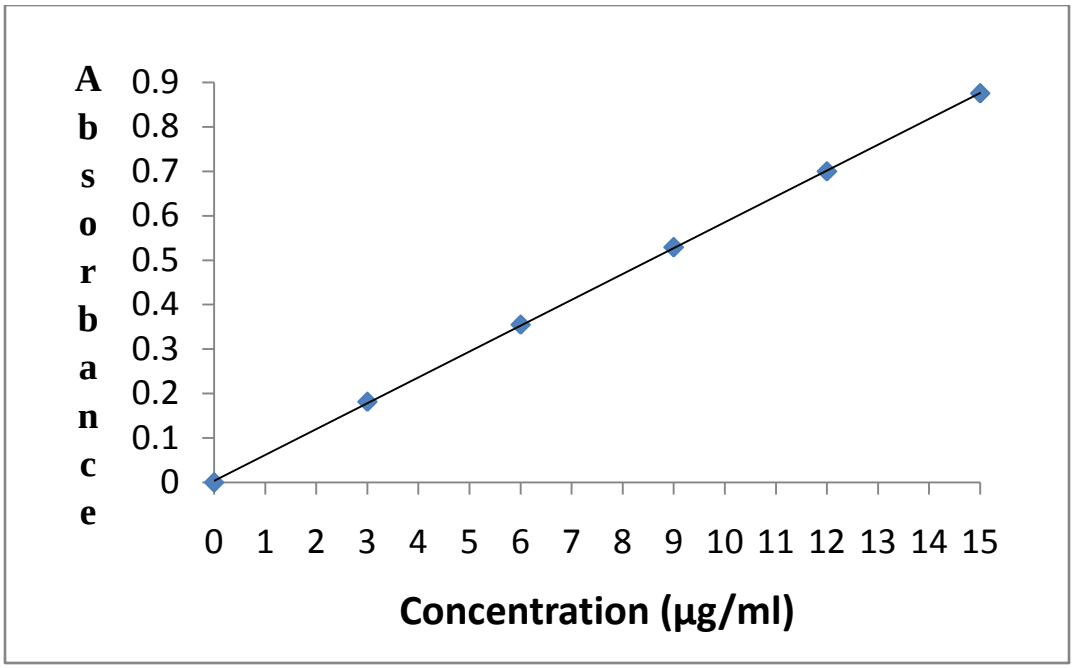



**Fig. 9.5:** Calibration curve of Ofloxacin in 0.1N HCl

The values of Correlation coefficient (R), Slope, Intercept obtained from the calibration curve are given in the Table 9.7.

**Table 9.7:** Data for Calibration Curve parameters of Ofloxacin in 0.1N HCl

| Sl. No. | Parameters | Values |
|---|---|---|
| 1 | Slope | 0.0570 |
| 2 | Intercept | 0.0089 |
| 3 | Correlation coefficient (R) | 0.9999 |

### 9.1.6. Loss on drying:

The percentage loss on drying after 5 hours was found to be 0.0797%. The sample passes test for loss on drying as per the limits specified in USP. (NMT 0.2%).

## 9.1.DRUG - POLYMERS COMPATIBILITY STUDIES:

### 9.2.2. Differential Scanning Calorimetry (DSC):

A

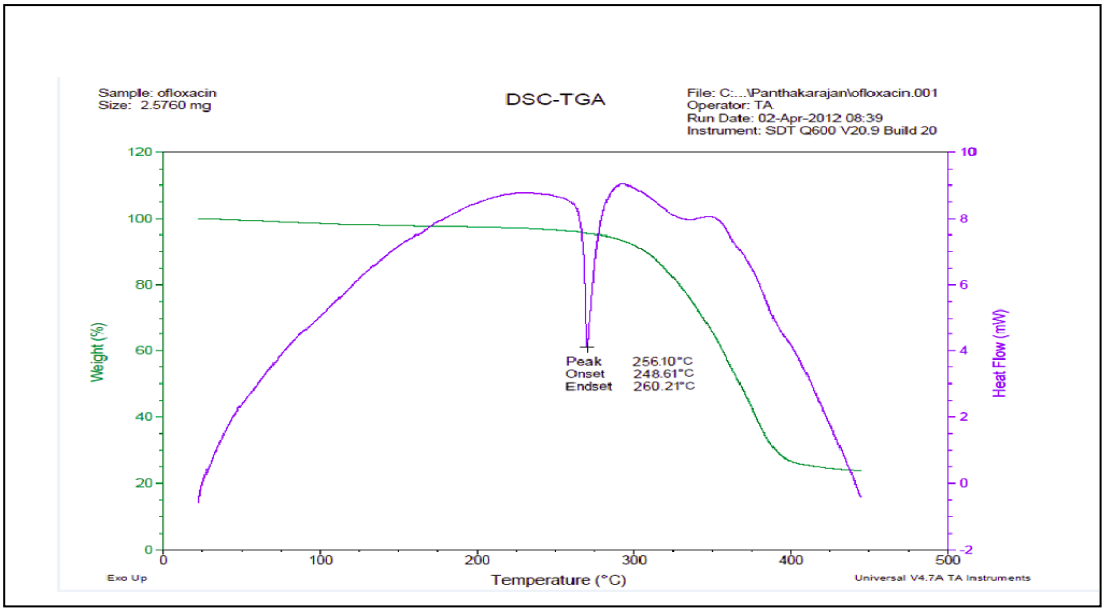



**Fig 9.6:** DSC Thermogram of Ofloxacin

B.

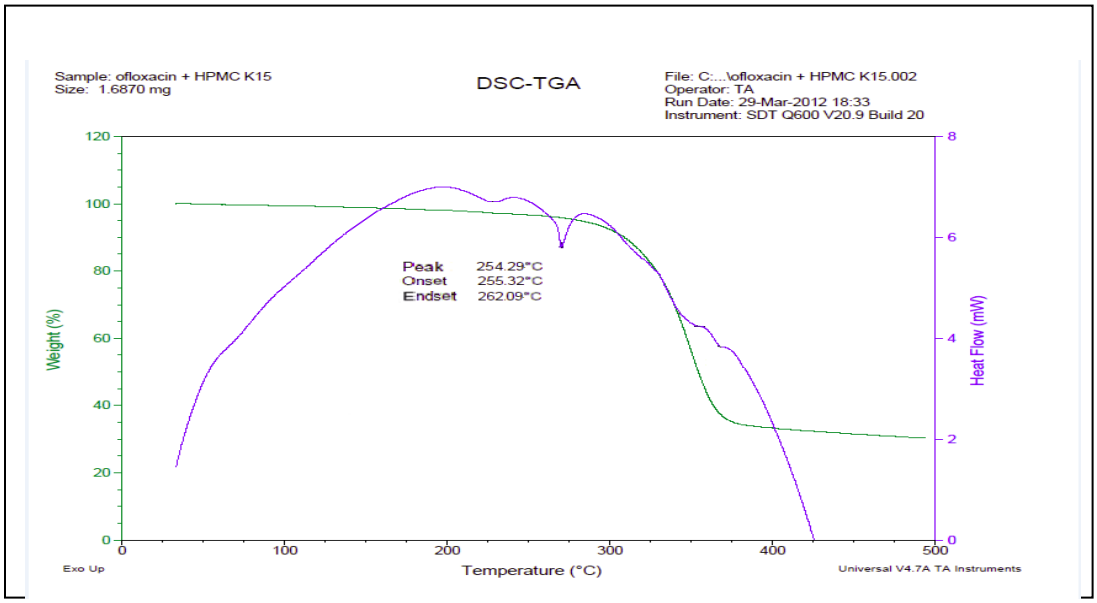



**Fig 9.7:** DSC Thermogram of Ofloxacin+HPMC K15

C.

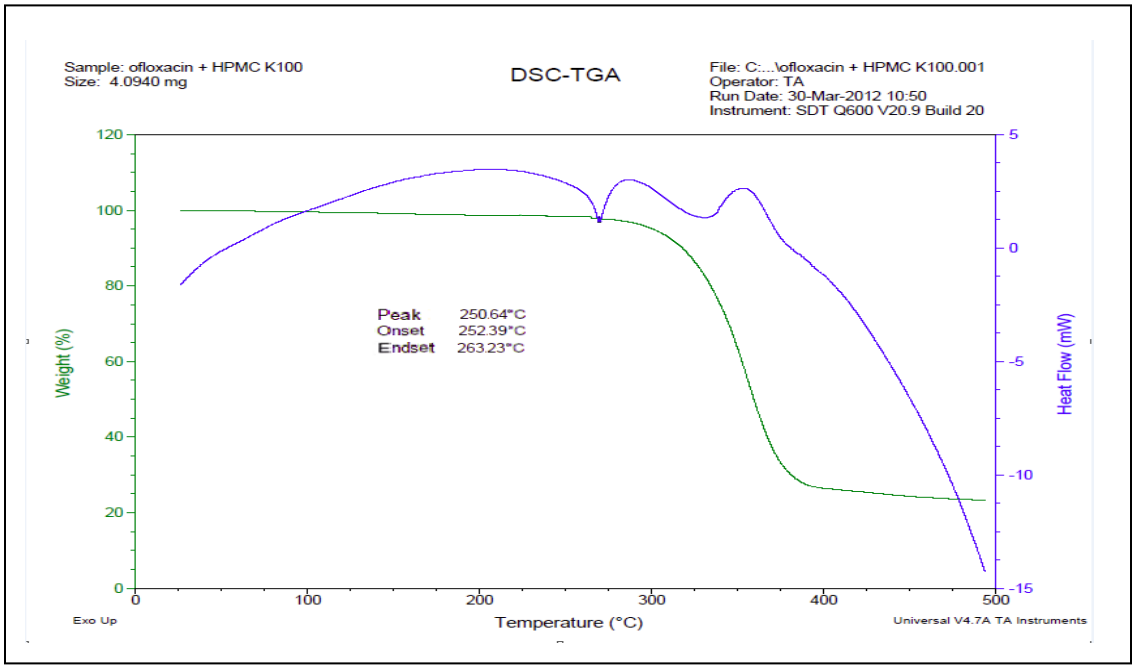



**Fig 9.8:** DSC Thermogram of Ofloxacin+ HPMC K 100

The results of DSC studies are given in above figures 9.6, 9.7, 9.8. Pure Ofloxacin showed sharp endotherm at 256.10°C corresponding to its melting point. There was no appreciable change in the melting endotherms of Ofloxacin with HPMCK15, Ofloxacin with HPMCK100, as compared to the thermogram of Ofloxacin. So, it could be concluded that there is no interaction between Ofloxacin and Polymers used in the formulations.

## 9.2. EVALUATION OF MICROMERITIC PROPERTIES OF POWDER BLENDS:

**Table 9.8:** Micromeritic Properties of Prepared Powder blends

| Formulations Code | Angle of Repose ($^{o}$) | LBD (gm/ml) | TBD (gm/ml) | Carr's Index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| **F1** | 24.268± 0.405 | 0.468± 0.012 | 0.520±0.001 | 9.803± 0.015 | 1.107± 0.001 |
| **F2** | 25.120± 0.440 | 0.484± 0.026 | 0.541±0.003 | 10.360± 0.020 | 1.114± 0.001 |
| **F3** | 25.336± 0.941 | 0.492± 0.014 | 0.540±0.002 | 8.826± 0.040 | 1.096± 0.001 |
| **F4** | 24.182± 0.336 | 0.476± 0.023 | 0.571±0.001 | 16.440.± 0.040 | 1.196± 0.001 |
| **F5** | 24.883± 0.886 | 0.476± 0.023 | 0.542±0.002 | 12.003± 0.015 | 1.117± 0.001 |
| **F6** | 25.386± 0.820 | 0.484± 0.014 | 0.600±0.002 | 19.306± 0.005 | 1.256± 0.001 |
| **F7** | 25.623± 0.812 | 0.469± 0.026 | 0.599±0.001 | 21.593± 0.050 | 1.254± 0.001 |
| **F8** | 23.875± 0.353 | 0.484± 0.026 | 0.599±0.001 | 19.053± 0.050 | 1.234± 0.001 |
| **F9** | 25.153± 0.881 | 0.461± 0.012 | 0.599±0.001 | 20.900± 0.020 | 1.236± 0.001 |

All the values are expressed as a mean ± SD., n = 3

### 9.2.1. Angle of repose:

The results for angle of repose are recorded in Table 9.8. Angle of repose ranged from 23.875 ± 0.353 to 25.386 ± 0.820. The flow properties of powder blends in all formulations exhibit good flow.

### 9.2.2. Bulk density and Tapped bulk density:

The results are shown in Table 9.8. The values of BD and TBD were found to be in the range from 0.600 ±0.002 to 0.520 ± 0.001 gm/ml and 0.461±0.012 to 0.492± 0.014 gm/ml respectively. So, it shows that all formulations having good flow properties and packability.

### 9.2.3. Carr's Compressibility Index:

The results for Carr's Compressibility Index are recorded in Table 9.8.The Carr's Compressibility Index were in the ranged from 9.803 ± 0.015 to 20.900 ± 0.020 %. This indicates good flow properties of powder.

### 9.2.4. Hausner's ratio:

The result were summarized in Table 9.8.The Hausner's ratio were found in the ranged from 1.107 ± 0.001 to 1.256 ± 0.001. So it indicates good flow properties.

## 9.3.EVALUATION OF TABLETS:

### 9.4.1. Evaluation of Physicochemical properties of tablets

**Table 9.9:** PhysicoChemical Properties of Tablets

| Formulations Code | Thickness* (mm) | Weight Variation*** (%) | Hardness** (kg/cm$^2$) | Friability* (%) | Drug Content* (%) |
|---|---|---|---|---|---|
| **F1** | 8.97±0.048 | 0.191±0.135 | 3.50±0.097 | 0.308±0.096 | 99.20±0.040 |
| **F2** | 8.94±0.052 | 0.136±0.091 | 3.49±0.120 | 1.090±0.030 | 97.20±0.040 |
| **F3** | 8.50±0.527 | 0.169±0.166 | 3.66±0.084 | 0.341±0.074 | 95.17±0.080 |
| **F4** | 8.85±0.306 | 0.190±0.084 | 3.75±0.053 | 0.529±0.025 | 90.36±0.120 |
| **F5** | 8.77±0.0408 | 0.167±0.133 | 3.56±0.097 | 0.891±0.023 | 88.25±0.040 |
| **F6** | 8.87±0.309 | 0.145±0.073 | 3.15±0.242 | 0.893±0.008 | 87.32±0.090 |
| **F7** | 8.94±0.070 | 0.158±0.117 | 4.48±0.676 | 0.330±0.052 | 86.32±0.050 |
| **F8** | 8.98±0.042 | 0.147±0.90 | 3.27±0.437 | 0.300±0.008 | 83.95±0.078 |
| **F9** | 8.97±0.048 | 0.146±0.077 | 3.56±0.097 | 0.570±0.940 | 82.29±0.150 |

*****All the values are expressed as a mean ± SD., n = 3

** All the values are expressed as a mean ± SD., n=9

***All the values are expressed as a mean ± SD., n=20

**9.3.1.1.Appearance:**

The tablets were observed visually and did not show any defects such as capping, chipping and lamination after punching.

**9.3.1.2.Thickness:**

The thickness of formulations ranged from 8.85 ± 0.306 mm to 8.98 ± 0.042 . The values are recorded in Table 9.9.

**9.3.1.3.Weight Variation:**

The percentage deviation from average tablet weight for all the formulations ranged from 0.136±0.091 to 0.190±0.135 %. The results are within the specified limits and showed in Table 9.9. Hence all formulations complied with the test for weight variation as per IP.

**9.3.1.4.Hardness:**

The results of Hardness of tablets were recorded in Table 9.9. It was found that the values are ranged from 3.15 ± 0.097 to 4.48 ± 0.676 kg/cm$^2$. Hardness values were satisfactory and indicated good mechanical strength of tablets.

**9.3.1.5. Friability:**

The Percentage Friability of all the formulations showed in Table 9.9. The results are ranged from 0.390±0.030 to 0.893±0.008%. So, the percentage loss of Friability of all the formulations was found to be less than 1 %.

### 9.3.1.6. Drug content:

Drug content was found to be uniform among different batches of tablets and ranged from 82.29 ± 0.15 to 99.20 ± 0.04%. These results showed that the all formulations having percentage drug content within the specified limits as per USP.

### 9.3.2. *IN VITRO* BUOYANCY STUDIES:

### 9.3.2.1. Floating lag time:

**Table 9.10:** *In vitro* buoyancy studies

| Formulation code | Floating lag time (s) | Total floating time (h) |
|---|---|---|
| F1 | 36.5±0.25 | >12 |
| F2 | 34.6±0.35 | >12 |
| F3 | 32.5±0.30 | >12 |
| F4 | 30.8±0.31 | >12 |
| F5 | 29.4±0.25 | >12 |
| F6 | 28.2±0.30 | >12 |
| F7 | 26.2±0.35 | >12 |
| F8 | 25.4±0.35 | >12 |
| F9 | 24.6±0.25 | >12 |

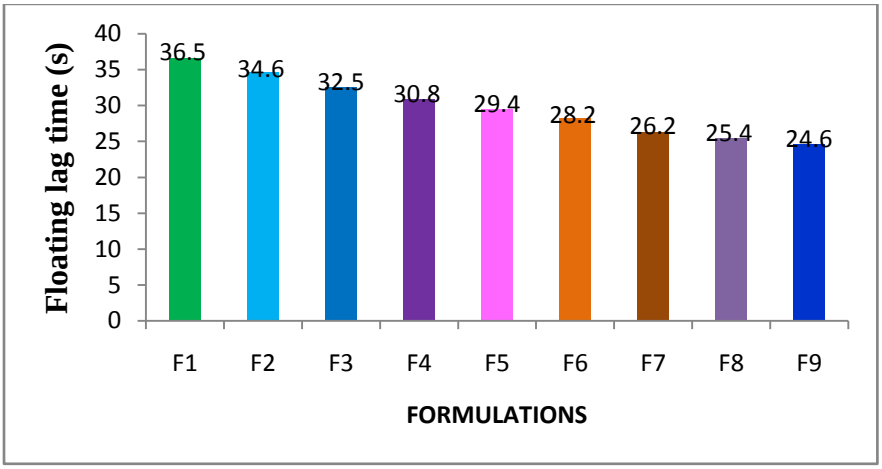
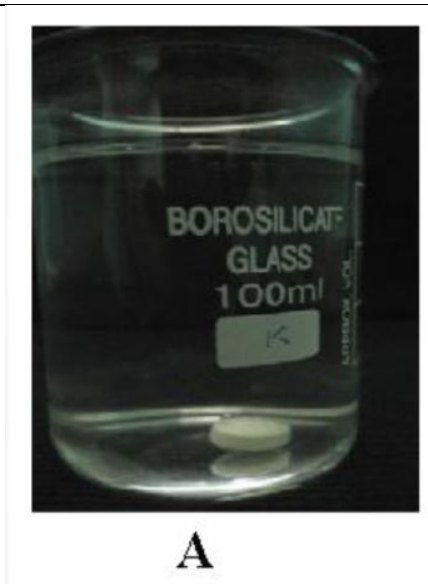


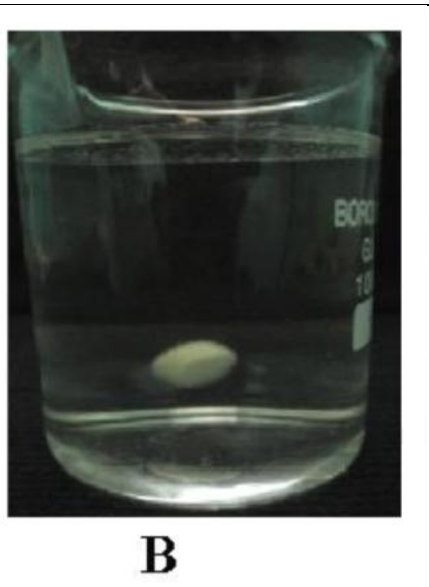

**Fig 9.9:** Comparision of Floating lag time studies for different formulations (F1-F9)

Floating lag time of formulations F1-F9



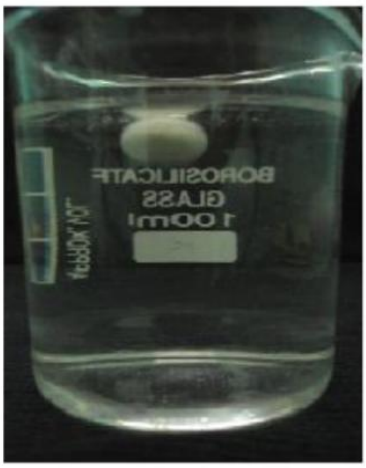

A

**Fig 9.10:** Floating lag time at initial stage



B

**Fig 9.11:** Tablet start to rise up to the surface



C

**Fig 9.12:** Floating lag time at 36.50 sec


D

**Fig 9.13:** Floating lag time after 12 hrs

The investigated gastric floating system employed sodium carbonate as a gas generating agent dispersed in hydro gel matrix (HPMCK15,HPMCK100). The in-vitro test revealed the ability of most formulation to maintain buoyant more than 12 hrs and shown in fig 9.9.This suggests that the gel layers, formed by the investigated polymers enabled efficient entrapment of generated gas bubbles. The possible increase in tablet porosity made it float on the test medium (0.1N HCl) for this extended period of time.

These matrices are fabricated so that upon on arrival in the stomach. Carbondioxide gas is liberated by the acidity of gastric contents and is entrapped in a gellified hydro colloid. A decrease in specific gravity passes the dosage form to float on the surface of the medium. The extended residence time of drug in stomach could cause increased absorption due to the fact that deuodenum was the main absorption site for Ofloxacin. One of the factor influencing behaviour of effervescent system is their floating lag time. As shown in the table 9.10 the, HPMC and SLS ratio has a marked effect on floating lag time of all the formulations prepared with a constant sodium bicarbonate ratio (10%w/w).

The floating lag time of formulation F1, F2 and F3 was found to be 36.5, 34.6, 32.5 respectively. 30.8, 29.4 and 28.2 for F4, F5 and F6. 26.2, 25.4 and 24.6 for F7,F8 and F9 respectively.

This above phenomena might be due to the generation of large amounts of effervescence with 10% sodium bicarbonate. This would lead to an increasing rate of pore formation and consequently rapid hydration of tablets.

### 9.3.3. SWELLING INDEX STUDY:

❖ Swelling Index data of formulation F1, F2, F3**:**

**Table 9.11**: Swelling Index data of formulation F1, F2, F3

| Sl. No. | Time (hours) | Swelling Index | | |
|---|---|---|---|---|
| | | F1 | F2 | F3 |
| 1 | 0 | 0.000 | 0.000 | 0.000 |
| 2 | 1 | 1.74±0.152 | 1.59±0.035 | 1.25±0.031 |
| 3 | 2 | 1.91±0.0301 | 1.91±0.030 | 1.53±0.042 |
| 4 | 3 | 2.04±0.151 | 2.19±0.053 | 1.69±0.030 |
| 5 | 4 | 2.21±0.030 | 2.40±0.041 | 1.91±0.022 |
| 6 | 5 | 2.59±0.112 | 2.53±0.032 | 2.13±0.030 |
| 7 | 6 | 3.02±0.054 | 2.92±0.030 | 2.63±0.041 |
| 8 | 7 | 3.10±0.042 | 2.99±0.073 | 2.91±0.072 |
| 9 | 8 | 3.35±0.030 | 3.21±0.022 | 2.64±0.032 |
| 10 | 9 | 3.23±0.070 | 3.03±0.040 | 2.49±0.030 |
| 11 | 10 | 2.97±0.091 | 2.87±0.030 | 2.27±0.031 |
| 12 | 11 | 2.81±0.031 | 2.71±0.052 | 2.08±0.053 |
| 13 | 12 | 2.79±0.040 | 2.70±0.031 | 2.07±0.030 |

All the values are expressed as a mean ± SD., n = 3

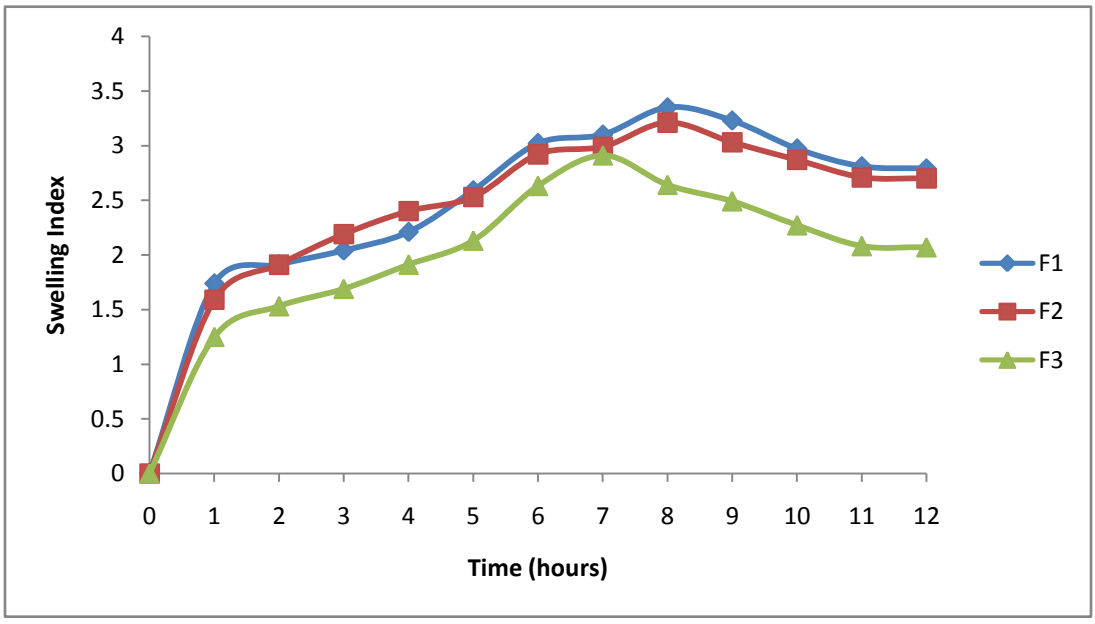



**Fig 9.14:** Swelling index of formulations F1, F2, F3

**Swelling Index data of formulation F4, F5, F6:**

**Table 9.12:** Swelling Index data of formulation F4, F5, F6

| Sl. No. | Time (hours) | Swelling Index | | |
|---|---|---|---|---|
| | | F4 | F5 | F6 |
| 1 | 0 | 0.000 | 0.000 | 0.000 |
| 2 | 1 | 1.12±0.030 | 0.97±0.043 | 0.76±0.033 |
| 3 | 2 | 1.49±0.042 | 1.21±0.031 | 0.92±0.030 |
| 4 | 3 | 1.76±0.040 | 1.34±0.072 | 1.02±0.040 |
| 5 | 4 | 1.89±0.030 | 1.63±0.025 | 1.26±0.076 |
| 6 | 5 | 2.02±0.033 | 1.70±0.030 | 1.42±0.129 |
| 7 | 6 | 2.17±0.030 | 1.95±0.021 | 1.66±0.030 |
| 8 | 7 | 2.45±0.029 | 2.18±0.150 | 2.04±0.040 |
| 9 | 8 | 2.93±0.040 | 2.74±0.030 | 1.95±0.051 |
| 10 | 9 | 2.82±0.031 | 2.58±0.054 | 1.83±0.050 |
| 11 | 10 | 2.69±0.030 | 2.27±0.031 | 1.62±0.030 |
| 12 | 11 | 2.46±0.034 | 2.03±0.044 | 1.54±0.021 |
| 13 | 12 | 2.45±0.032 | 2.01±0.041 | 1.53±0.040 |

All the values are expressed as a mean ± SD., n = 3

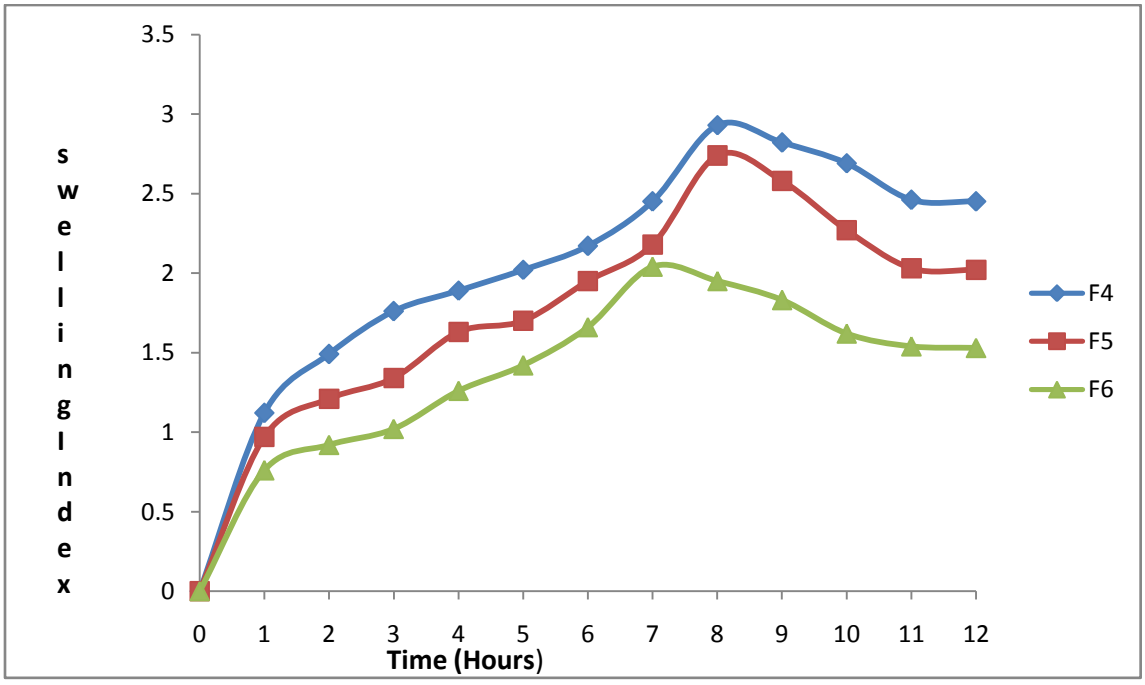



**Fig 9.15**: Swelling Index data of formulation F4, F5, F6

**Table 9.13:** Swelling Index data of formulation F7, F8, F9

| Sl. No. | Time (hours) | Swelling Index | | |
|---|---|---|---|---|
| | | F7 | F8 | F9 |
| 1 | 0 | 0.000 | 0.000 | 0.000 |
| 2 | 1 | 0.75±0.302 | 0.71±0.022 | 0.69±0.022 |
| 3 | 2 | 0.95±0.040 | 0.92±0.020 | 0.89±0.032 |
| 4 | 3 | 1.04±0.030 | 1.01±0.031 | 0.99±0.043 |
| 5 | 4 | 1.46±0.055 | 1.36±0.050 | 1.32±0.012 |
| 6 | 5 | 1.62±0.012 | 1.52±0.030 | 1.49±0.050 |
| 7 | 6 | 2.04±0.020 | 1.99±0.0312 | 1.96±0.032 |
| 8 | 7 | 2.96±0.090 | 2.76±0.0570 | 2.61±0.030 |
| 9 | 8 | 1.81±0.054 | 1.79±0.021 | 1.72±0.041 |
| 10 | 9 | 1.69±0.061 | 1.66±0.033 | 1.64±0.070 |
| 11 | 10 | 1.57±0.030 | 1.58±0.030 | 1.52±0.021 |
| 12 | 11 | 1.52±0.040 | 1.44±0.70 | 1.40±0.026 |
| 13 | 12 | 1.48±0.022 | 1.42±0.061 | 1.37±0.030 |

All the values are expressed as a mean ± SD., n = 3

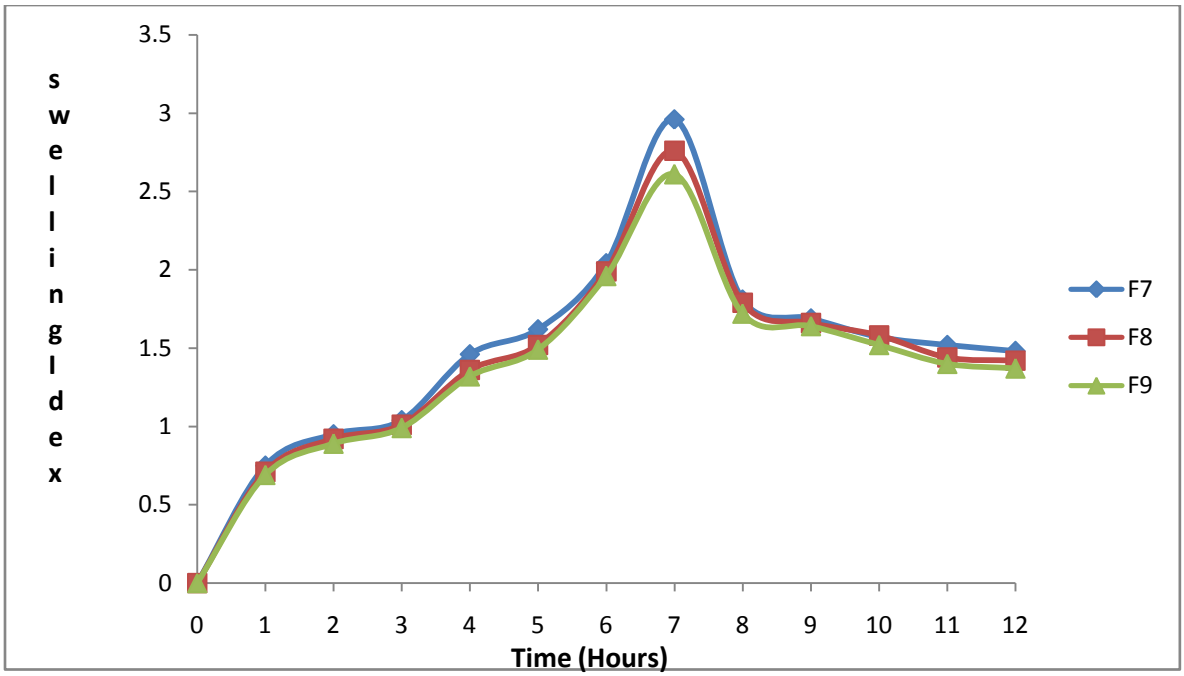



**Fig 9.16:** Swelling index of formulations F7, F8, F9

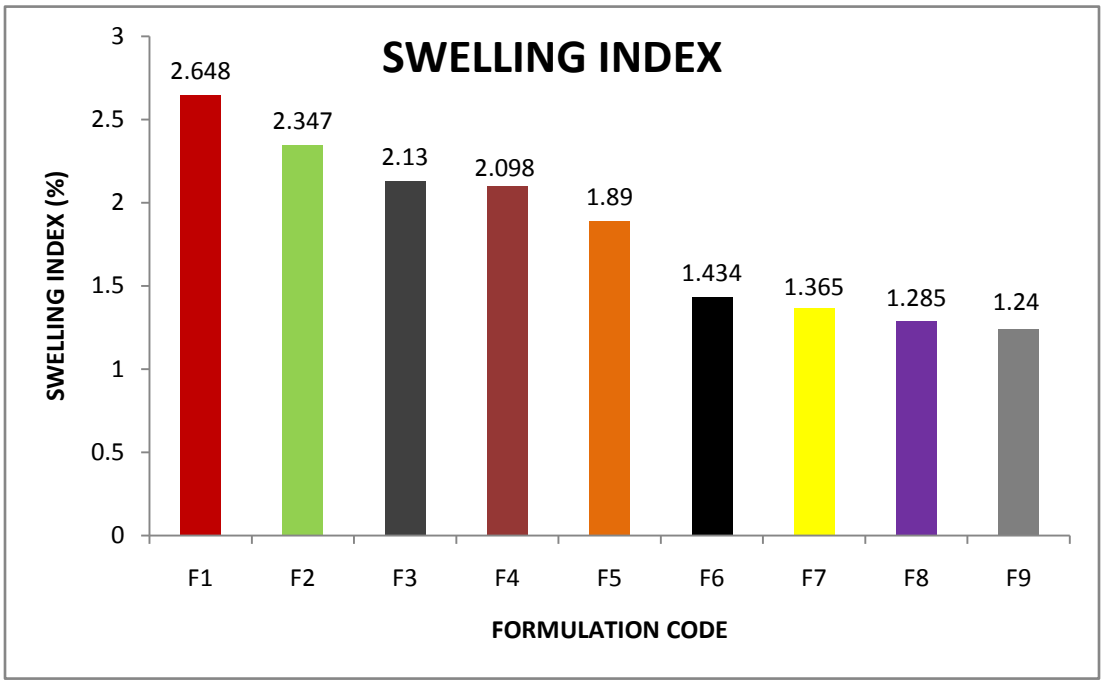



**Fig. 9.17:** Comparison of swelling Index of formulations F1-F9

The floating and drug release profile are dependent upon swelling behaviour of the tablets. Swelling index increased as the weight gained by the tablet increased proportionally with the rate of hydration.

Swelling is also a vital factor to ensure buoyancy and drug dissolution of matrix tablet. The floating tablet containing HPMCK15 and HPMCK100.

The comparative swelling Index data of all the formulations were showed in Figure 29. From this Figure, it can be observed that the swelling Index of different formulations decreased in the following order;

**F1> F2 > F3 > F4 > F5 > F6 > F7 > F8>F9**

### 9.3.4. *IN VITRO* DRUG RELEASE STUDIES:

### 9.4.3.1. *IN VITRO* DRUG RELEASE PROFILE OF TABLETS:

- **Drug release profile for Formulation F1:**

**Table 9.14:** *In vitro* drug release data of Formulation F1

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 029.51 | 07.38±0.040 | 0.00 | 0.50 |
| 3 | | 2 | 062.81 | 15.72±0.010 | 0.01 | 1.03 |
| 4 | | 3 | 096.23 | 24.06±0.041 | 0.02 | 1.53 |
| 5 | | 4 | 129.59 | 32.40±0.090 | 0.02 | 2.04 |
| 6 | | 5 | 162.95 | 40.74±0.030 | 0.03 | 2.54 |
| 7 | | 6 | 196.32 | 49.08±0.033 | 0.03 | 3.04 |
| 8 | | 7 | 229.68 | 57.42±0.060 | 0.04 | 3.55 |
| 9 | | 8 | 263.04 | 65.76±0.030 | 0.04 | 4.05 |
| 10 | | 9 | 296.40 | 74.11±0.010 | 0.05 | 4.55 |
| 11 | | 10 | 329.77 | 82.42±0.080 | 0.05 | 5.05 |
| 12 | | 11 | 363.10 | 90.78±0.021 | 0.06 | 5.56 |
| 13 | | 12 | 393.49 | 99.12±0.020 | 0.06 | 6.06 |

All the values are expressed as a mean ± SD., n = 3

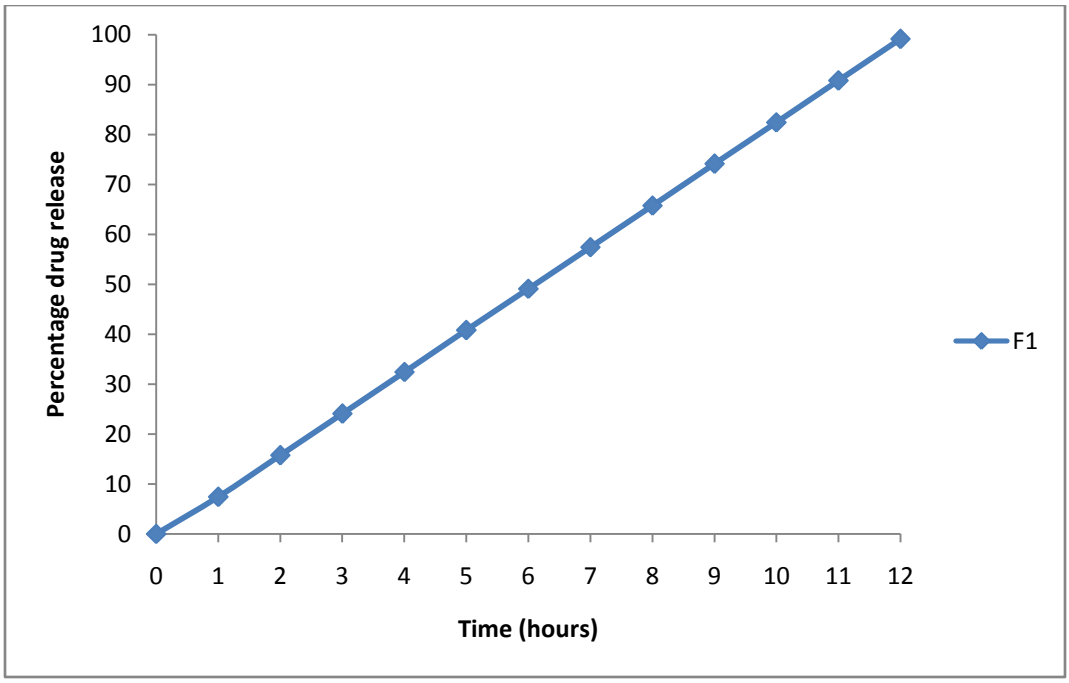



**Fig 9.18 :** Percentage drug release profile of formulation F1

❖ **Drug release profile for Formulation F2:**

**Table 9.15:** *In vitro* drug release profile data of Formulation F2

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 28.64 | 07.16±0.030 | 0.01 | 0.50 |
| 3 | | 2 | 61.14 | 15.28±0.011 | 0.01 | 1.03 |
| 4 | | 3 | 93.63 | 23.41±0.032 | 0.02 | 1.54 |
| 5 | | 4 | 126.13 | 31.53±0.043 | 0.02 | 2.04 |
| 6 | | 5 | 158.62 | 39.66±0.051 | 0.03 | 2.54 |
| 7 | | 6 | 191.12 | 47.78±.0410 | 0.03 | 3.05 |
| 8 | | 7 | 223.61 | 55.90±0.030 | 0.04 | 3.55 |
| 9 | | 8 | 256.11 | 64.03±0.050 | 0.04 | 4.05 |
| 10 | | 9 | 288.60 | 72.15±0.021 | 0.05 | 4.55 |
| 11 | | 10 | 321.10 | 80.28±0.043 | 0.05 | 5.05 |
| 12 | | 11 | 353.60 | 88.40±0.080 | 0.06 | 5.56 |
| 13 | | 12 | 386.09 | 96.52±0.030 | 0.06 | 6.06 |

All the values are expressed as a mean ± SD., n = 3

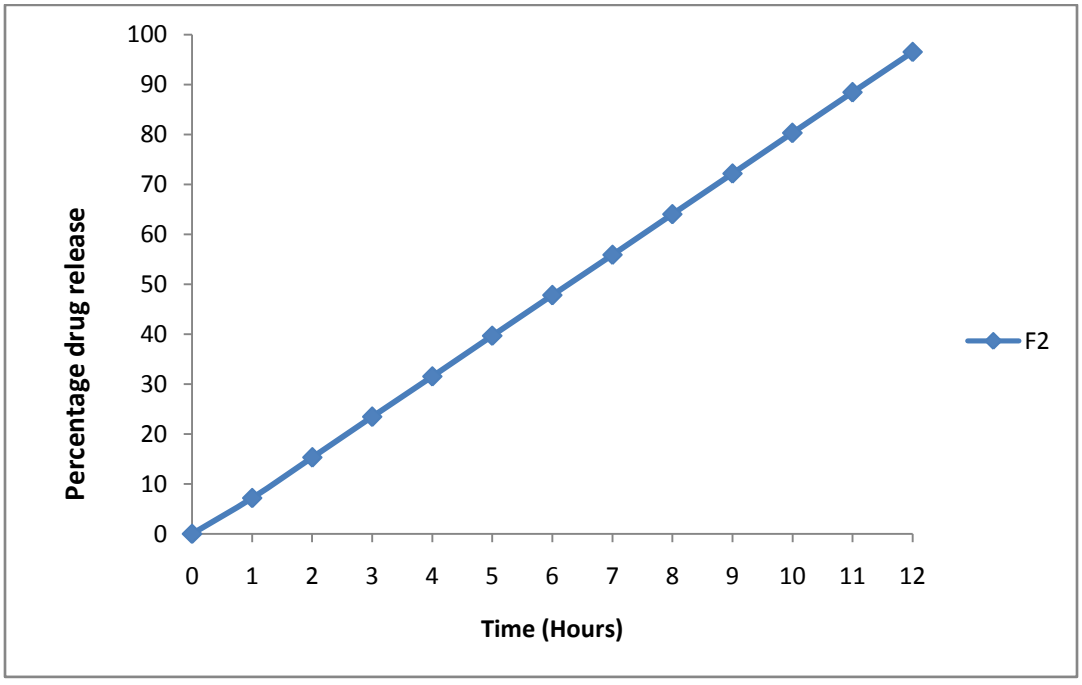



**Fig 9.19:** percentage drug release profile of formulation F2

❖ **Drug release profile for Formulation F3:**

**Table 9.16:** *In vitro* drug release data of Formulation F3

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 28.10 | 07.02±0.031 | 0.01 | 0.50 |
| 3 | | 2 | 60.05 | 15.01±0.041 | 0.01 | 1.03 |
| 4 | | 3 | 92.01 | 23.00±0.041 | 0.01 | 1.54 |
| 5 | | 4 | 123.96 | 30.99±0.012 | 0.02 | 2.03 |
| 6 | | 5 | 155.91 | 38.98±0.030 | 0.02 | 2.54 |
| 7 | | 6 | 187.87 | 46.97±0.010 | 0.03 | 3.04 |
| 8 | | 7 | 219.82 | 54.96±0.060 | 0.03 | 3.54 |
| 9 | | 8 | 251.78 | 62.94±0.042 | 0.04 | 4.06 |
| 10 | | 9 | 283.73 | 70.93±0.053 | 0.04 | 4.53 |
| 11 | | 10 | 315.68 | 78.92±0.041 | 0.05 | 5.03 |
| 12 | | 11 | 347.64 | 86.91±0.032 | 0.05 | 5.58 |
| 13 | | 12 | 379.59 | 94.90±0.029 | 0.06 | 6.08 |

All the values are expressed as a mean ± SD., n = 3

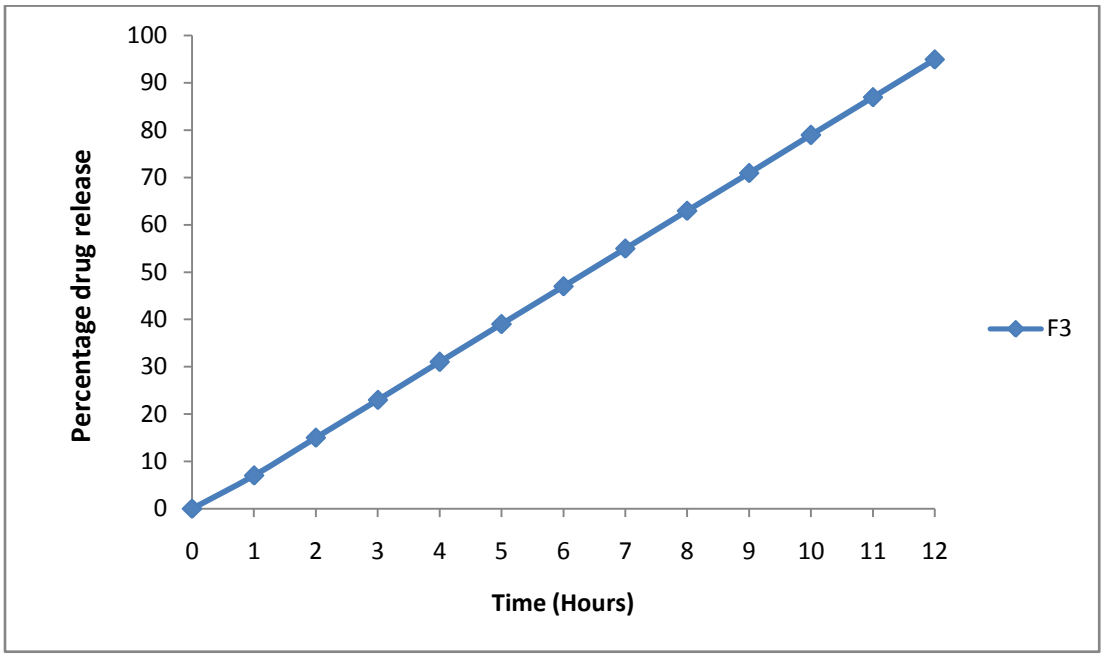



**Fig. 9.20:** Percentage drug release profile of formulation F3

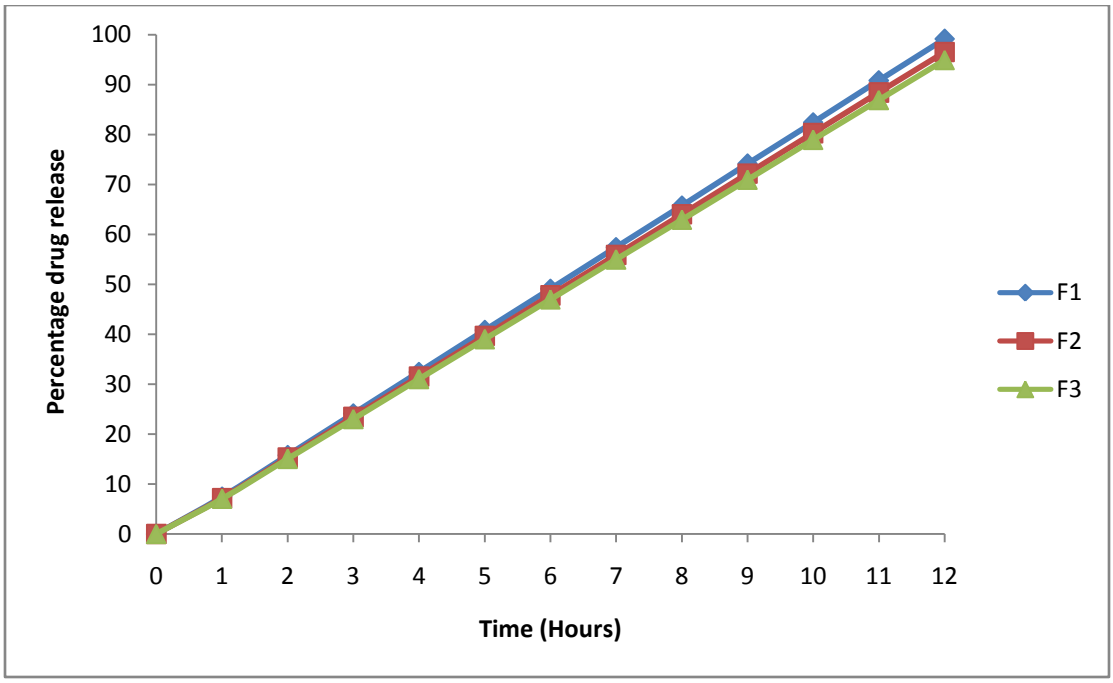



**Fig 9.21:** Comparision of percentage drug release of formulation F1, F2, F3

❖ **Drug Release Profile for Formulation F4:**

**Table 9.17:** *In vitro* drug release data of Formulation F4

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 0.086 | 08.35±0.020 | 0.01 | 0.50 |
| 3 | | 2 | 0.172 | 17.67±0.010 | 0.01 | 1.02 |
| 4 | | 3 | 0.258 | 26.98±0.050 | 0.02 | 1.53 |
| 5 | | 4 | 0.344 | 36.30±0.040 | 0.02 | 2.03 |
| 6 | | 5 | 0.430 | 45.61±0.030 | 0.03 | 2.54 |
| 7 | | 6 | 0.516 | 54.93±0.041 | 0.04 | 3.03 |
| 8 | | 7 | 0.602 | 64.24±0.030 | 0.04 | 3.54 |
| 9 | | 8 | 0.688 | 73.56±0.041 | 0.05 | 4.04 |
| 10 | | 9 | 0.774 | 82.81±0.031 | 0.05 | 4.54 |
| 11 | | 10 | 0.860 | 92.19±0.012 | 0.06 | 5.05 |
| 12 | | 11 | - | - | - | - |
| 13 | | 12 | - | - | - | - |

All the values are expressed as a mean ± SD., n = 3

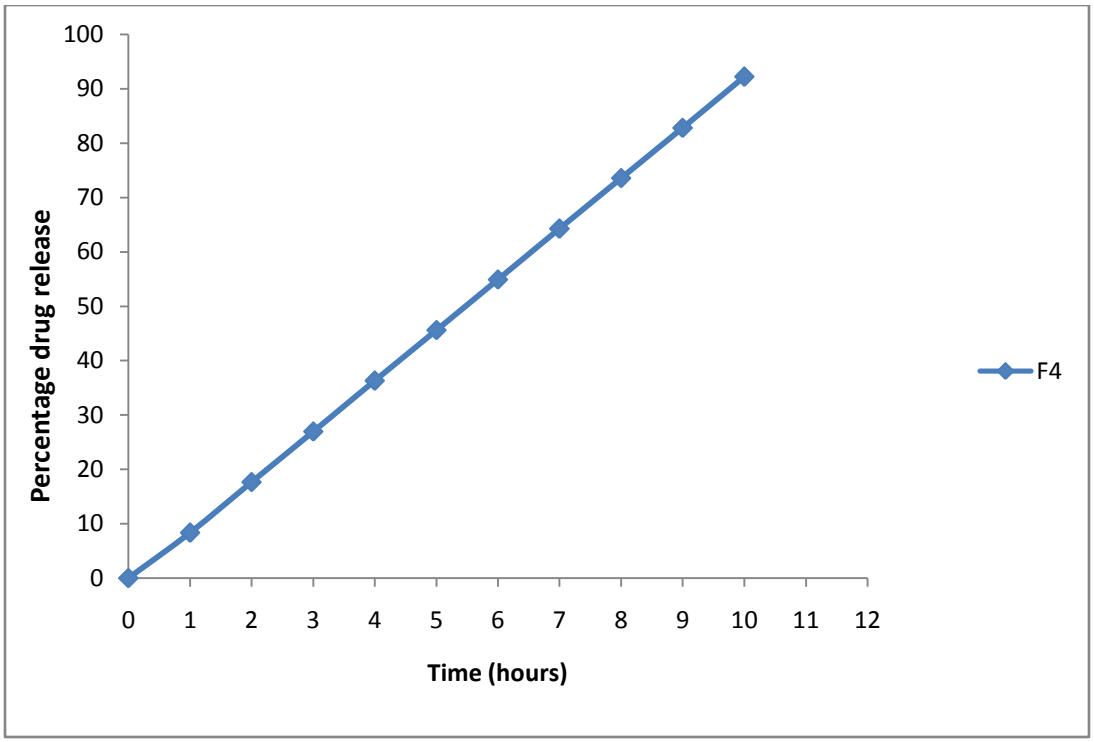



**Fig. 9.22:** Percentage drug release profile of formulation F4

❖ **Drug Release Profile for Formulation F5:**

**Table 9.18:** *In vitro* drug release data of Formulation F5

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 32.54 | 08.13±0.030 | 0.01 | 0.50 |
| 3 | | 2 | 68.93 | 17.23±0.031 | 0.01 | 1.02 |
| 4 | | 3 | 105.33 | 26.33±0.061 | 0.02 | 1.53 |
| 5 | | 4 | 141.72 | 35.45±0.040 | 0.02 | 2.04 |
| 6 | | 5 | 178.12 | 44.55±0.072 | 0.03 | 2.54 |
| 7 | | 6 | 214.51 | 53.63±0.051 | 0.03 | 3.03 |
| 8 | | 7 | 250.91 | 62.73±0.030 | 0.04 | 3.52 |
| 9 | | 8 | 287.31 | 71.83±0.050 | 0.05 | 4.00 |
| 10 | | 9 | 323.70 | 80.93±0.041 | 0.05 | 4.54 |
| 11 | | 10 | 360.10 | 90.02±0.020 | 0.06 | 5.04 |
| 12 | | 11 | - | - | - | - |
| 13 | | 12 | - | - | - | - |

All the values are expressed as a mean ± SD., n = 3

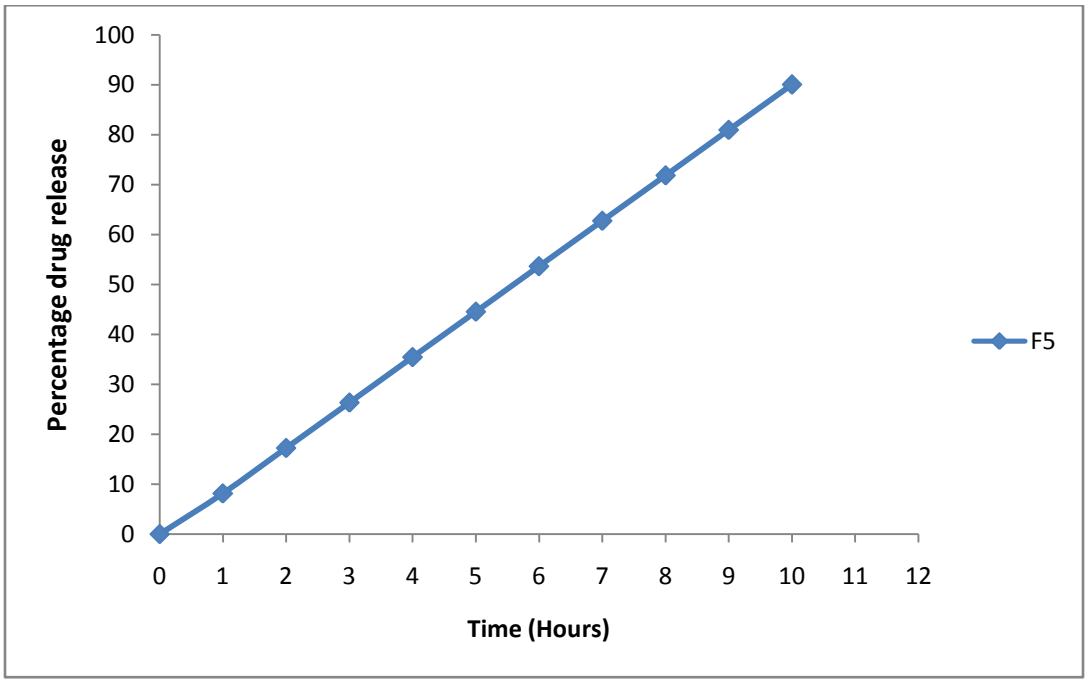



**Fig 9.23:** Percentage drug release profile of formulation F5

❖ **Drug Release Profile for Formulation F6:**

**Table 9.19:** *In vitro* drug release data of Formulation F6

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 32.43 | 08.11±0.905 | 0.01 | 0.50 |
| 3 | | 2 | 68.76 | 17.19±0.110 | 0.01 | 1.02 |
| 4 | | 3 | 105.07 | 26.27±0.036 | 0.02 | 1.53 |
| 5 | | 4 | 141.38 | 35.34±0.026 | 0.02 | 2.04 |
| 6 | | 5 | 177.69 | 44.42±0.032 | 0.03 | 2.53 |
| 7 | | 6 | 213.99 | 53.50±0.041 | 0.03 | 3.00 |
| 8 | | 7 | 250.30 | 62.58±0.040 | 0.04 | 3.58 |
| 9 | | 8 | 286.61 | 71.65±0.031 | 0.04 | 4.10 |
| 10 | | 9 | 322.92 | 80.73±0.051 | 0.05 | 4.67 |
| 11 | | 10 | 359.23 | 89.81±0.11 | 0.06 | 5.02 |
| 12 | | 11 | - | - | - | - |
| 13 | | 12 | - | - | - | - |

All the values are expressed as a mean ± SD., n = 3

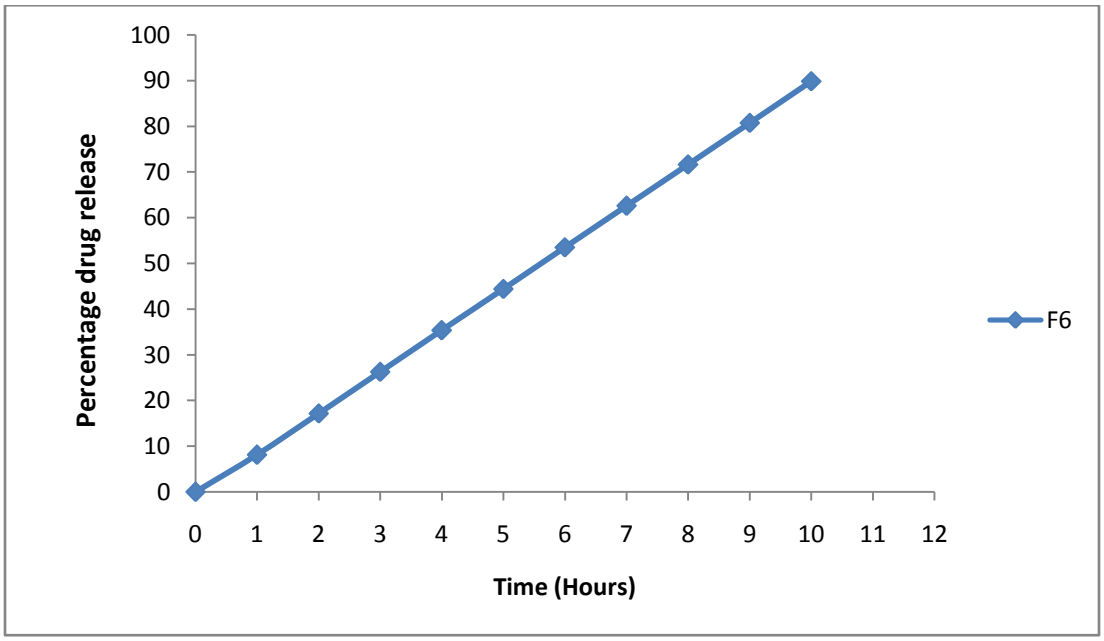



**Fig. 9.24.** Percentage drug release profile of formulation F6

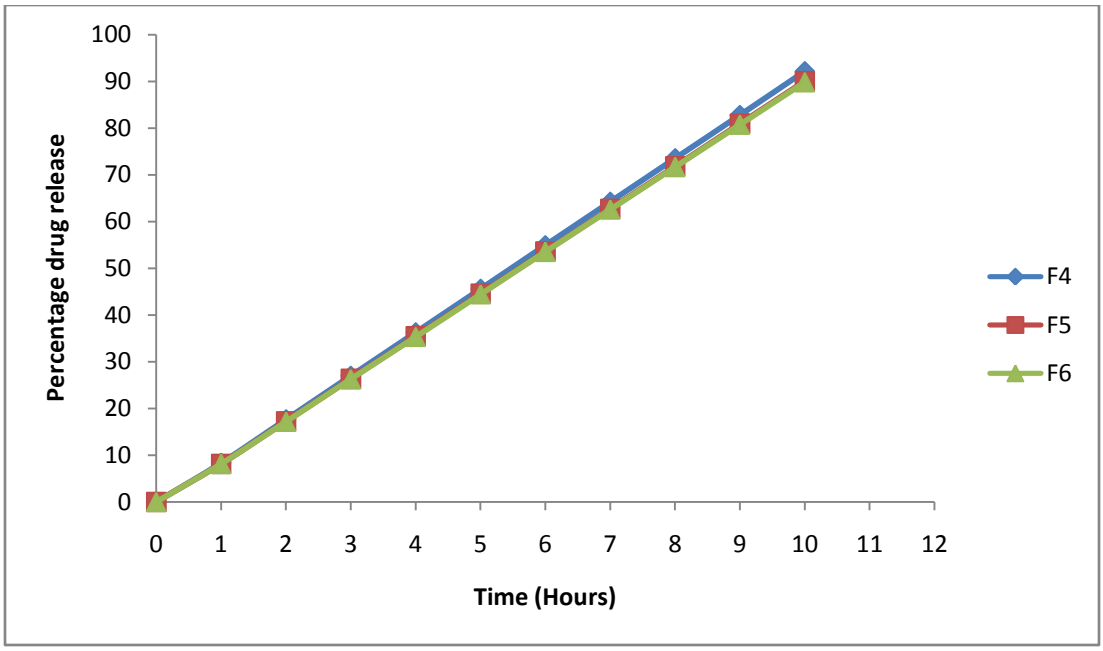



**Fig 9.25:** comparison of percentage drug release profile of formulation F4 ,F5, F6

❖ **Drug Release Profile for Formulation F7:**

**Table 9.20:** *In vitro* drug release data of Formulation F7

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 40.55 | 10.14±0.050 | 0.01 | 0.50 |
| 3 | | 2 | 84.97 | 21.24±0.031 | 0.01 | 1.02 |
| 4 | | 3 | 129.38 | 32.34±0.041 | 0.02 | 1.52 |
| 5 | | 4 | 173.79 | 43.45±0.031 | 0.03 | 2.03 |
| 6 | | 5 | 218.20 | 54.55±0.020 | 0.04 | 2.54 |
| 7 | | 6 | 262.61 | 65.65±0.081 | 0.04 | 2.94 |
| 8 | | 7 | 307.02 | 76.75±0.030 | 0.05 | 3.48 |
| 9 | | 8 | 351.43 | 87.86±0.051 | 0.06 | 4.09 |
| 10 | | 9 | - | - | - | - |
| 11 | | 10 | - | - | - | - |
| 12 | | 11 | - | - | - | - |
| 13 | | 12 | - | - | - | - |

All the values are expressed as a mean ± SD., n = 3

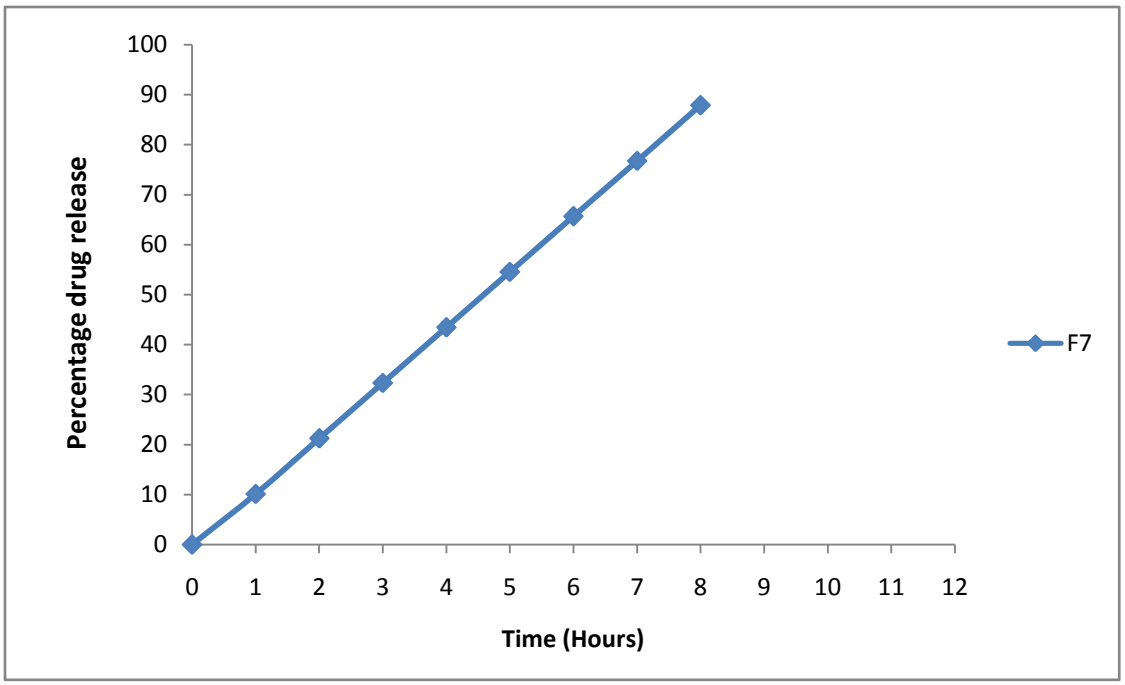



**Fig. 9.26.** Percentage drug release profile of formulation F7

❖ **Drug Release Profile for Formulation F8:**

**Table 9.21:** *In vitro* drug release data of Formulation F8

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 39.47 | 9.78±0.030 | 0.01 | 0.50 |
| 3 | | 2 | 82.80 | 20.70±0.041 | 0.01 | 1.02 |
| 4 | | 3 | 126.13 | 31.53±0.042 | 0.02 | 1.53 |
| 5 | | 4 | 169.45 | 42.36±0.020 | 0.03 | 2.08 |
| 6 | | 5 | 212.78 | 53.20±0.010 | 0.03 | 2.55 |
| 7 | | 6 | 256.12 | 64.03±0.031 | 0.04 | 3.07 |
| 8 | | 7 | 299.44 | 74.86±0.031 | 0.05 | 3.48 |
| 9 | | 8 | 342.76 | 85.69±0.021 | 0.06 | 3.99 |
| 10 | | 9 | - | - | - | - |
| 11 | | 10 | - | - | - | - |
| 12 | | 11 | - | - | - | - |
| 13 | | 12 | - | - | - | - |

All the values are expressed as a mean ± SD., n = 3

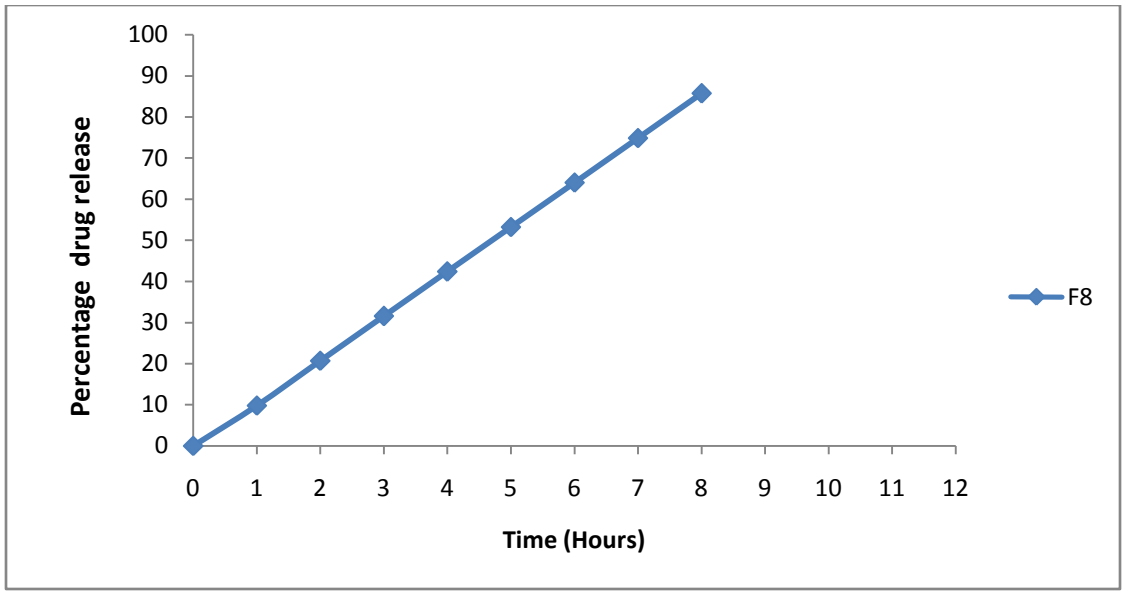



**Fig. 9.27:** Percentage drug release profile of formulation F8

❖ **Drug Release Profile for Formulation F9:**

**Table 9.22:** *In vitro* Drug release data for formulation F9

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 38.93 | 09.73±0.051 | 0.01 | 0.50 |
| 3 | | 2 | 81.72 | 20.31±0.012 | 0.01 | 1.02 |
| 4 | | 3 | 124.51 | 31.46±0.041 | 0.02 | 1.54 |
| 5 | | 4 | 167.29 | 42.23±0.022 | 0.03 | 2.04 |
| 6 | | 5 | 210.75 | 53.50±0.021 | 0.03 | 2.56 |
| 7 | | 6 | 252.82 | 64.21±0.030 | 0.04 | 3.05 |
| 8 | | 7 | 295.65 | 73.92±0.033 | 0.05 | 3.50 |
| 9 | | 8 | 338.43 | 84.61±0.050 | 0.06 | 4.01 |
| 10 | | 9 | - | - | - | - |
| 11 | | 10 | - | - | - | - |
| 12 | | 11 | - | - | - | - |
| 13 | | 12 | - | - | - | - |

All the values are expressed as a mean ± SD., n = 3

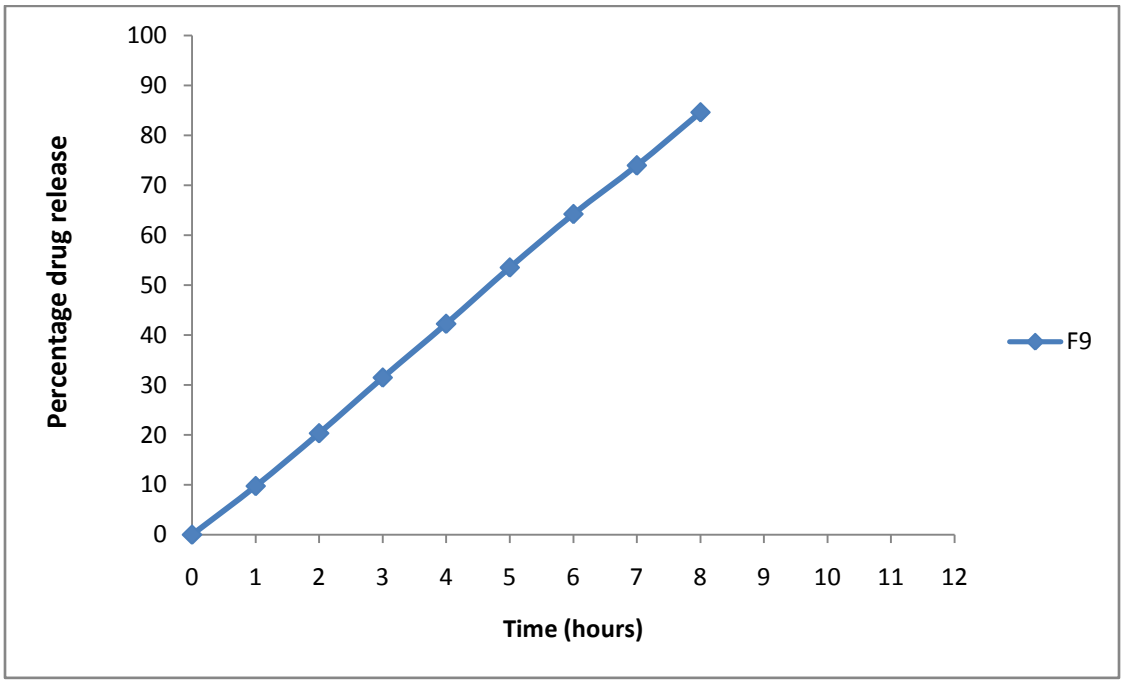



**Fig 9.28**: Percentage drug release of formulation F9

In-vitro dissolution studies of all the formulation of Ofloxacin intragastric tablets were carried out in 0.1 N HCl. The study was performed for 12 hrs and cumulative drug release was calculated at different time interval**.**

This showed that HPMC hydrated more rapidly with high amount of SLS in the presence of 0.1 N HCl. The formulation F1, F2 and F3 showed the drug release 99.12, 96.52 and 94.91% upto 12 hrs but F4, F5 and F6 showed the drug release 92.12, 90.06 and 89.80% upto 10 hrs and F7, F8 and F9 showed the drug release 87.81, 85.64 and 84.61 upto 8hrs**.**

The comparison graph for all formulations F1-F9 are also shown in following Fig 9.30

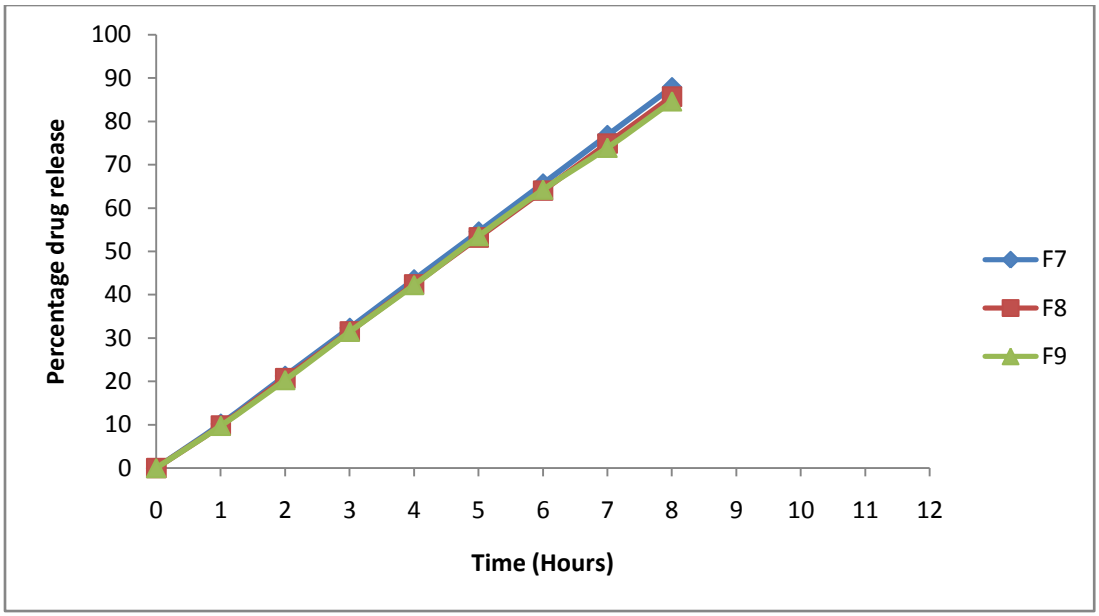



**Fig 9.29:** Comparison of percentage drug release of formulations F7, F8, F9

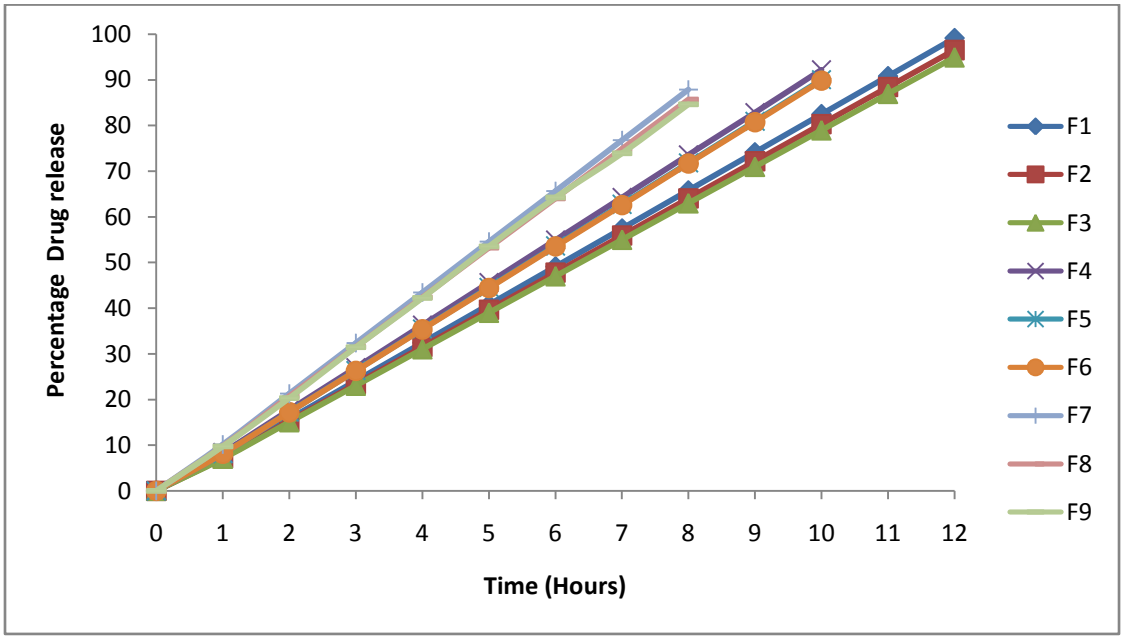



**Fig. 9.30:** percentage drug release profile of formulation F1 – F9

### 9.4.3.2.Kinetics of *In-vitro* Drug Release:

**Table 9.23:** Different Kinetic models for Formulations F1-F9

| Code | Zero order | | First order | | Higuchi | | Korsemayer-Peppas | | Best fit model |
|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | $K_0$ ($mg/h^{-1}$) | $R^2$ | $K_1$ ($h^{-1}$) | $R^2$ | K (mg $h^{-1/2}$) | $R^2$ | n | |
| F1 | 0.9999 | 0.0100 | 0.9999 | 0.0001 | 0.9237 | 0.025 | 0.9999 | 1.0356 | Peppas |
| F2 | 0.9999 | 0.0102 | 0.9999 | 0.0001 | 0.9236 | 0.0220 | 0.9999 | 1.0367 | Peppas |
| F3 | 0.9999 | 0.0103 | 0.9999 | 0.0001 | 0.9233 | 0.0290 | 0.9999 | 1.0347 | Peppas |
| F4 | 0.9999 | 0.0120 | 0.9999 | 0.0001 | 0.9259 | 0.0310 | 0.9999 | 1.0346 | Peppas |
| F5 | 0.9998 | 0.0117 | 0.9998 | 0.0001 | 0.9266 | 0.0304 | 0.9998 | 1.0367 | Peppas |
| F6 | 0.9994 | 0.0118 | 0.9994 | 0.0001 | 0.9226 | 0.0305 | 0.9999 | 1.0413 | Peppas |
| F7 | 0.9996 | 0.0141 | 0.9996 | 0.0001 | 0.9304 | 0.0328 | 0.9997 | 1.0220 | Peppas |
| F8 | 0.9997 | 0.0141 | 0.9997 | 0.0001 | 0.9308 | 0.0328 | 0.9997 | 1.0422 | Peppas |
| F9 | 0.9998 | 0.0138 | 0.9998 | 0.0001 | 0.9302 | 0.0322 | 0.9999 | 1.0367 | Peppas |

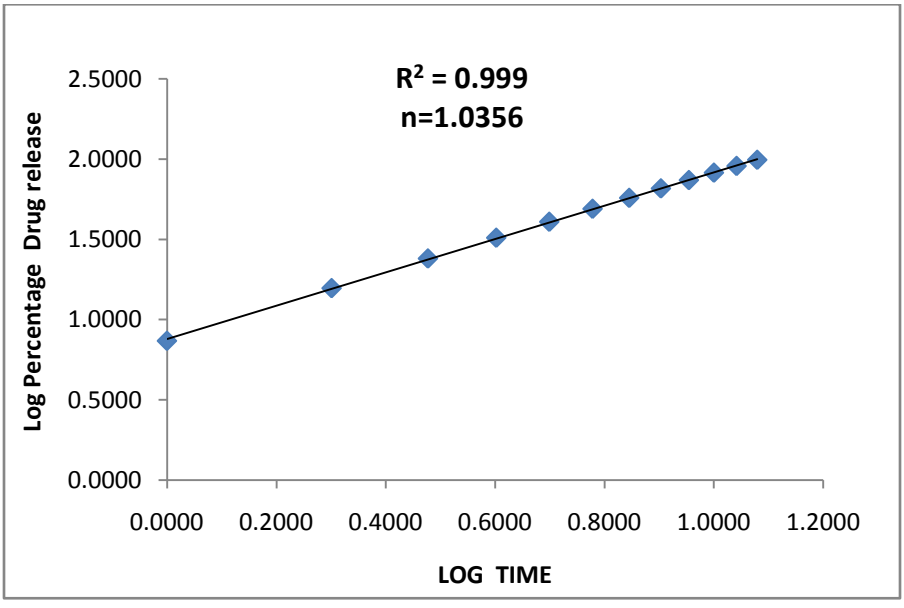



**Fig. 9.31:** Peppas plot of formulation F1

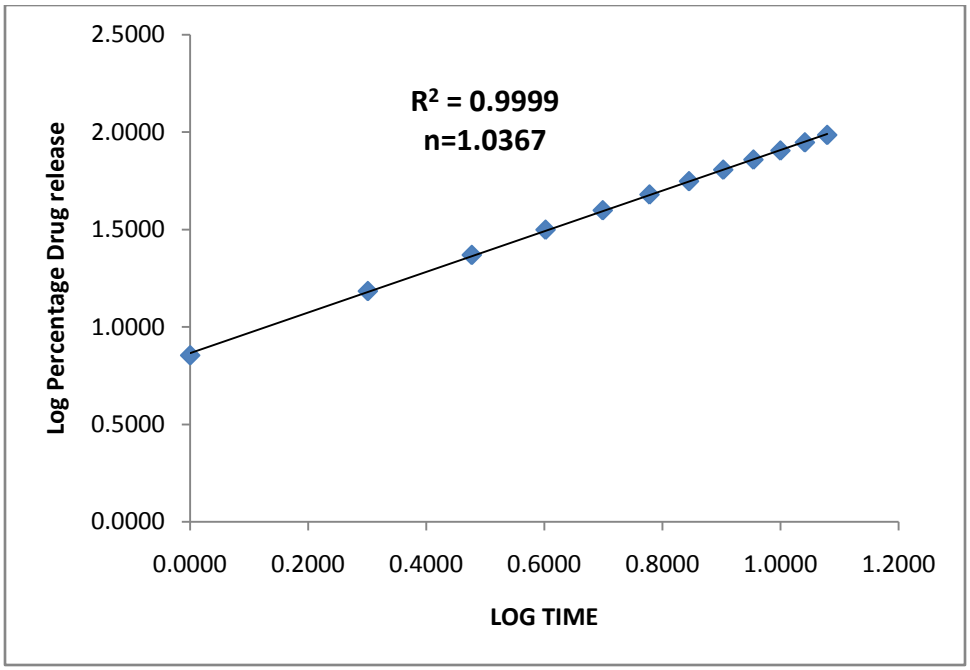



**Fig. 9.32**: Peppas plot of formulation F2

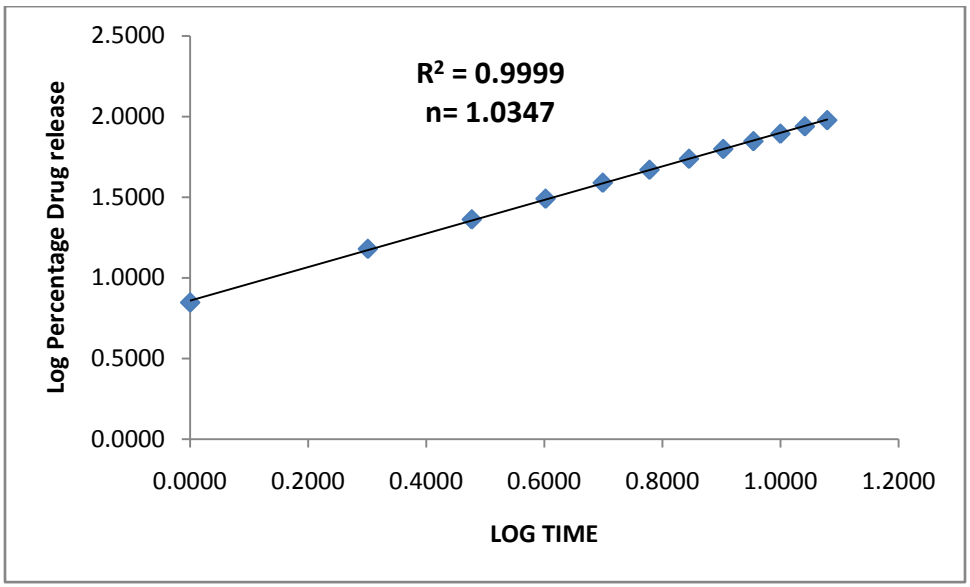



**Fig. 9.33:** Peppas plot of formulation F3

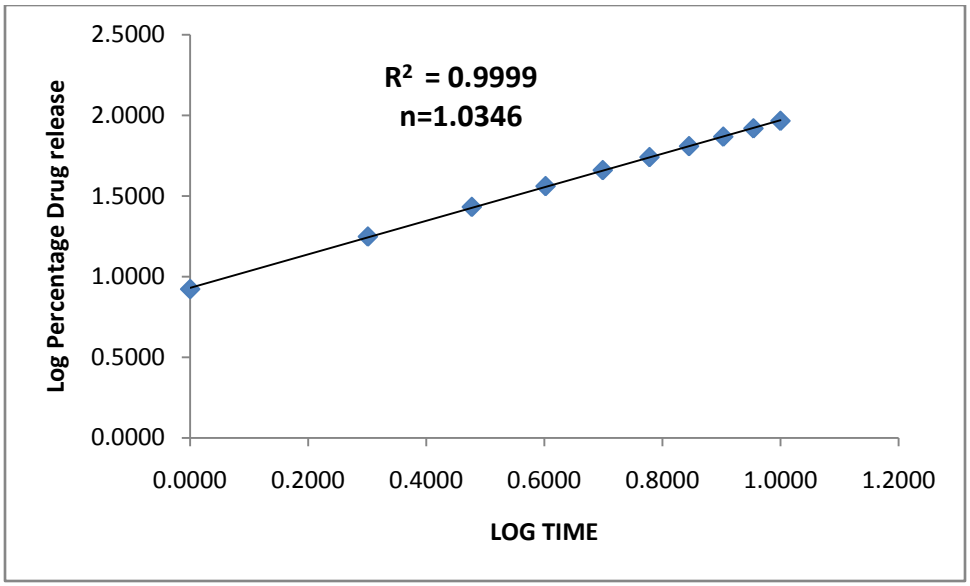



**Fig. 9.34:** Peppas plot of formulation F4

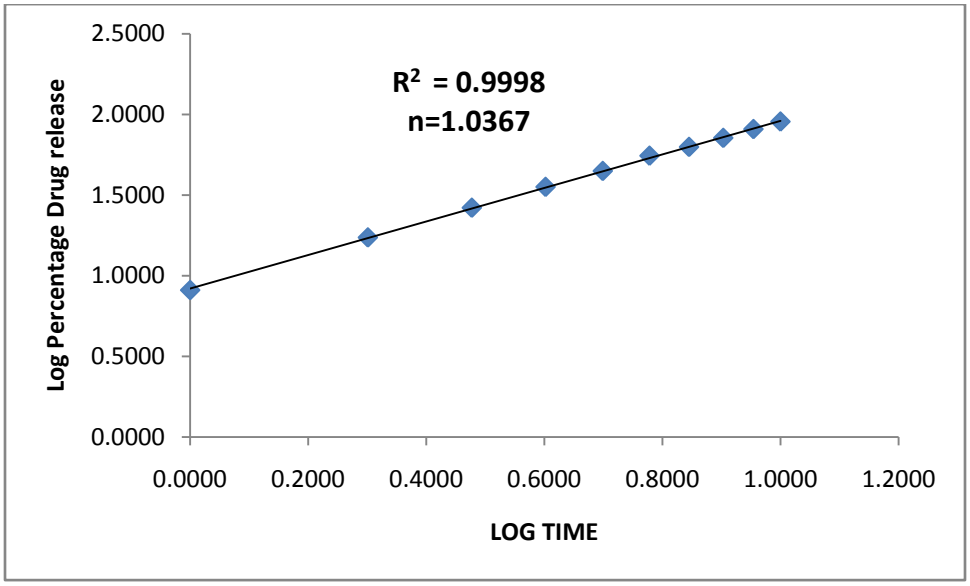



**Fig. 9.35:** Peppas plot of formulation F5

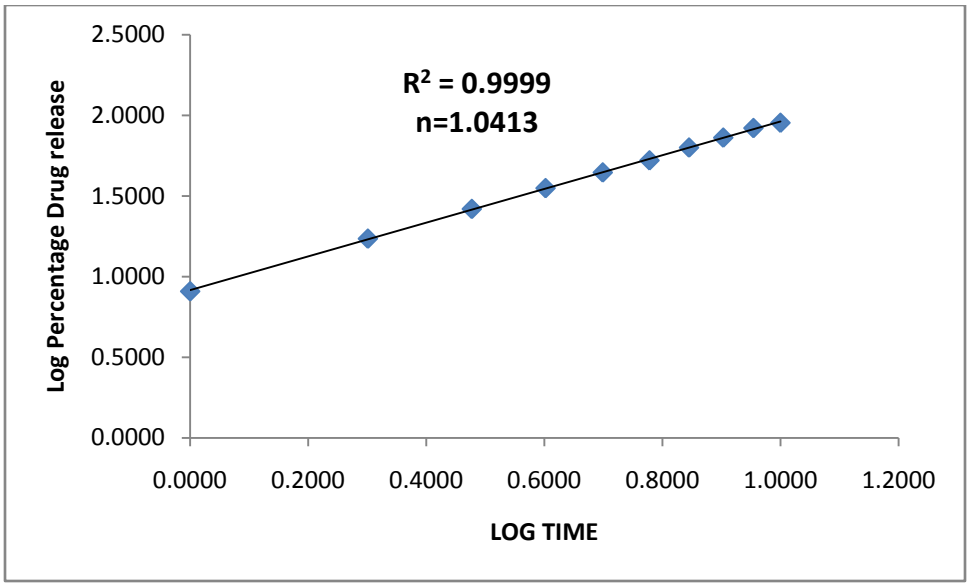



**Fig. 9.36:** Peppas plot of formulation F6

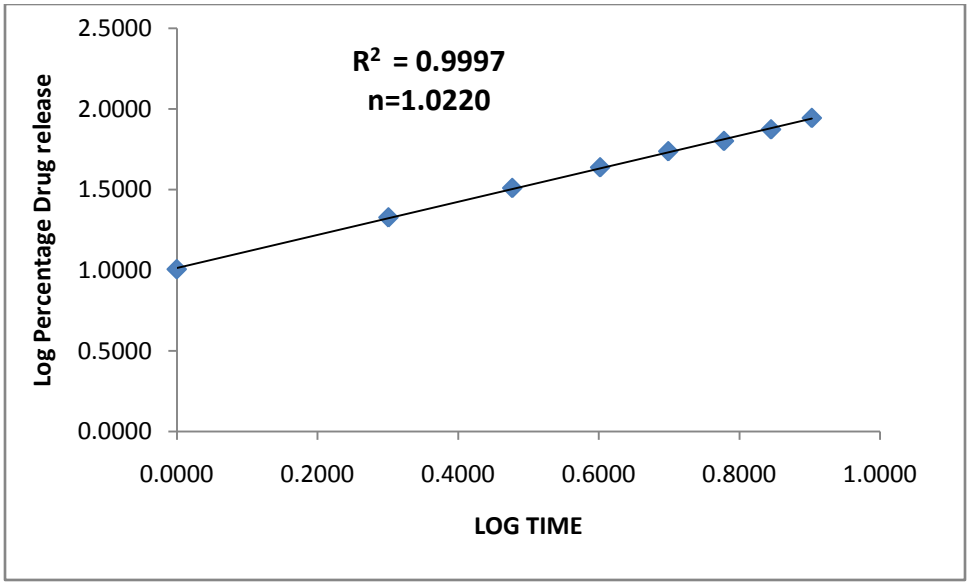



**Fig. 9.37:** Peppas plot of formulation F7

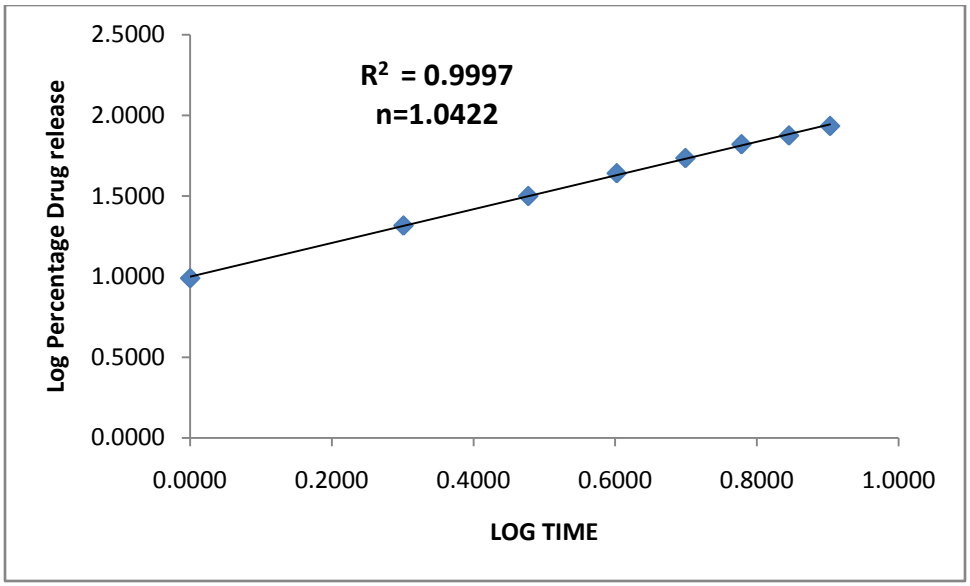



**Fig. 9.38:** Peppas plot of formulation F8

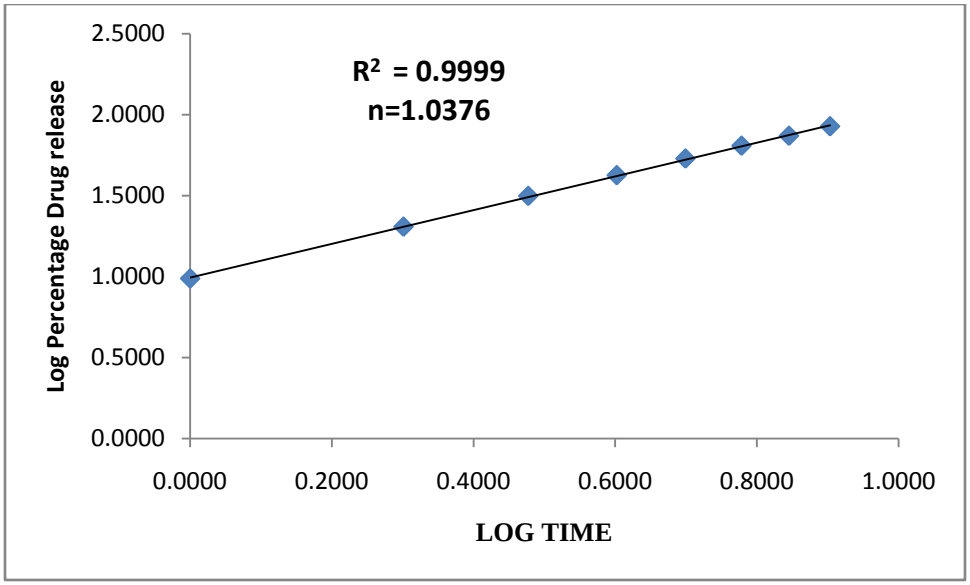



**Fig9.39:** Peppas plot of formulation F9

The data obtained from *invitro* drug release studies were fitted to zero order, first order, Higuchi, korsmeyers-peppas equation. To confirm the exact mechanism of the drug release korsmeyer and peppas equqtion superposes two apparently independent

mechanism of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer.

## 9.5. STABILITY STUDIES

From the results it was found that formulation F1 is the best formulation amongst the nine formulations. Thus formulation F1 was selected for stability studies.

### 9.5.1. Stability studies at the end of First month (30 days):

#### 9.5.1.1. Hardness:

The hardness of tablet after one month of stability studies was studied. The results are within the limits. The data is shown in Table 9.24.

**Table 9.24:** Hardness of formulation F1 at the end of one month of stability

| Sl. No. | Formulation | Hardness ($kg/cm^2$) |
|---|---|---|
| 1. | F1 | 3.42± 0.032 |

All the values are expressed as a mean ± SD., n = 6

#### 9.5.1.2. Drug Content :

The Percentage drug content of tablet after one month of stability studies was studied. The results are within the official limits. The data is shown in Table 9.25.

**Table 9.25:** Drug content of formulation F1 at the end of one month of stability

| Sl. No. | Formulation | Percentage drug content |
|---|---|---|
| 1. | F1 | 99.12± 0.060 |

All the values are expressed as a mean ± SD., n = 3

#### 9.5.1.3. *In vitro* Buoyancy Studies:

#### 9.5.1.3.1. Floating lag time:

The floating lag time of tablet after one month of stability studies was studied. The data was shown in the table 9.26

**Table 9.26**: Floating lag time of formulation F1 after one month stability

| Sl.No | Formulation | Floating lag time |
|---|---|---|
| 1. | F1 | 36.46±0.036 |

#### 9.5.1.3.2. Total Floating time:

The total floating time of tablet after one month study of stability was studied. It was found to be more than(>) 12 hrs.

#### 9.5.1.4. *In vitro* drug release study:

The percentage drug release from F1 tablet after one month of stability was studied. The data is shown in Table 9.27.

**Table 9.27:** *In vitro* drug release data of formulation F1 at the end of one month of stability

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0 | 0 | 0 | 0 |
| 2 | | 1 | 1.15 | 07.33±0.18 | 0.01 | 0.50 |
| 3 | | 2 | 2.48 | 15.67±0.040 | 0.01 | 1.02 |
| 4 | | 3 | 3.81 | 24.01±0.032 | 0.02 | 1.52 |
| 5 | | 4 | 5.14 | 32.35±0.045 | 0.02 | 2.03 |
| 6 | | 5 | 6.47 | 40.69±0.051 | 0.03 | 2.54 |
| 7 | | 6 | 7.80 | 48.89±0.045 | 0.03 | 2.94 |
| 8 | | 7 | 9.13 | 57.37±0.030 | 0.04 | 3.40 |
| 9 | | 8 | 10.46 | 65.71±0.060 | 0.04 | 4.09 |
| 10 | | 9 | 11.79 | 74.05±0.030 | 0.05 | 4.82 |
| 11 | | 10 | 13.12 | 82.39±0.055 | 0.05 | 5.05 |
| 12 | | 11 | 14.45 | 90.73±0.030 | 0.06 | 5.94 |
| 13 | | 12 | 15.78 | 99.07±0.032 | 0.06 | 6.02 |

All the values are expressed as a mean ± SD., n = 3

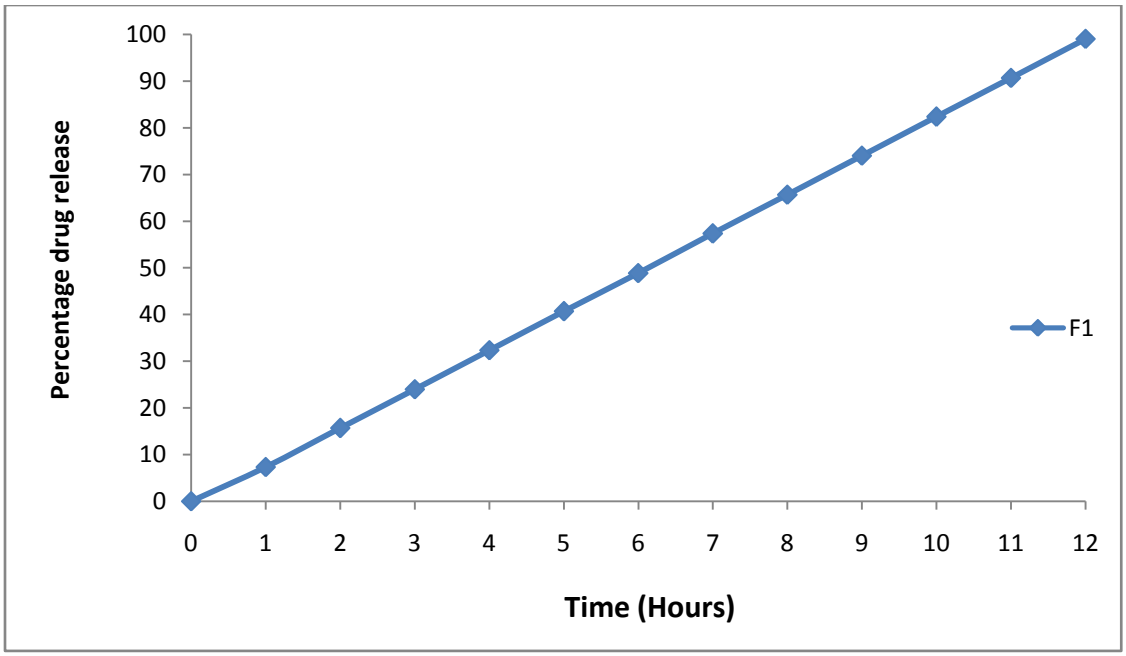



**Fig. 9.40:** *In vitro* drug release profile of formulation F1 at the end of 1 month of stability

### 9.5.2. Stability studies at the end of Second month (60 days):

#### 9.5.2.1. Hardness:

The hardness of tablet after Two months of stability studies was studied. The results are within the limits. The data is shown in Table 9.28.

**Table 9.28:** Hardness of formulation F1 at the end of two months of stability

| Sl. No. | Formulation | Hardness (kg/cm$^2$) |
|---|---|---|
| 1. | F1 | 3.40± 0.095 |

All the values are expressed as a mean ± SD., n = 3

#### 9.5.2.2. Drug content:

The Percentage drug content of tablet after Two months of stability studies was studied. The results are within the official limits. The data is shown in Table 9.29.

**Table 9.29:** Drug content of formulation F1 at the end of two months of stability

| Sl. No. | Formulation | Percentage drug content |
|---|---|---|
| 1. | F1 | 99.10 ±0.030 |

All the values are expressed as a mean ± SD., n = 3

**9.5.2.3.*In vitro* Buoyancy Studies:**

**9.5.2.4. 1 Floating lag time:**

The floating lag time of tablet after two months of stability studies was studied. The data was shown in the table 9.30

**Table 9.30**: Floating lag time of formulation F1 after two months stability

| Sl.No | Formulation | Floating lag time |
|---|---|---|
| 1. | F1 | 36.39±0.005 |

**9.5.2.3.2. Total Floating time:**

The total floating time of tablet after two months study of stability was studied. It was found to be more than(>) 12 hrs.

**9.5.2.4. *In vitro* dissolution study:**

The Percentage Drug Release from F2 tablet after Two months of stability was studied. The data is shown in Table 9.31.

**Table 9.31:** *In vitro* drug release data of formulation F1 at the end of two months of stability

| \Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 1.12 | 7.30±0.026 | 0.01 | 0.50 |
| 3 | | 2 | 2.45 | 15.64±0.030 | 0.01 | 1.02 |
| 4 | | 3 | 3.57 | 23.98±0.045 | 0.02 | 1.52. |
| 5 | | 4 | 4.90 | 32.32±0.015 | 0.02 | 2.03 |
| 6 | | 5 | 6.23 | 40.66±0.037 | 0.03 | 2.54 |
| 7 | | 6 | 7.56 | 49.00±0.030 | 0.03 | 2.94 |
| 8 | | 7 | 8.89 | 57.34±0.045 | 0.04 | 3.48 |
| 9 | | 8 | 10.22 | 65.68±0.040 | 0.04 | 4.09 |
| 10 | | 9 | 11.55 | 74.02±0.056 | 0.05 | 4.82 |
| 11 | | 10 | 12.88 | 82.36±0.035 | 0.05 | 5.02 |
| 12 | | 11 | 14.21 | 90.70±0.015 | 0.06 | 5.92 |
| 13 | | 12 | 15.54 | 99.04±0.025 | 0.06 | 6.06 |

All the values are expressed as a mean ± SD., n = 3

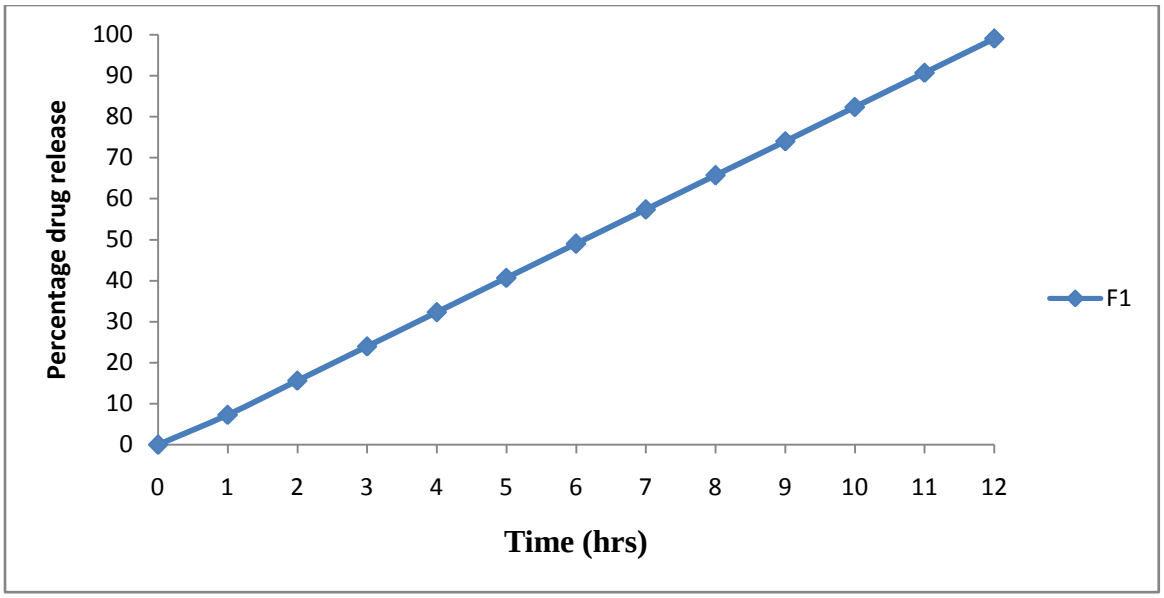



**Fig. 9.41:** *In vitro* Drug release profile of formulation F1 at the end of 2 months of stability

### 9.5.3. Stability studies at the end of Three months (90 days):

#### 9.5.3.1.Hardness:

The hardness of tablet after Three months of stability studies was studied. The results are within the limits. The data is shown in Table 9.32.

**Table 9.32:** Hardness of formulation F1 at the end of three months of stability

| Sl. No. | Formulation | Hardness (kg/cm$^2$) |
|---|---|---|
| 1. | F1 | 3.39±0.035 |

All the values are expressed as a mean ± SD., n = 3

#### 9.5.3.2.Drug content:

The Percentage drug content of tablet after Third month of stability studies was studied. The results are within the official limits. The data is shown in Table 9.33.

**Table 9.33:** Drug content of formulation F1 at the end of three months of stability

| Sl. No. | Formulation | Percentage drug content |
|---|---|---|
| 1. | F1 | 99.08 ±0.031 |

All the values are expressed as a mean ± SD., n = 3

**9.5.3.3. *In vitro* Buoyancy Studies:**

**9.5.3.3.1. Floating lag time:**

The floating lag time of tablet after three months of stability studies was studied. The data was shown in the table 9.34

**Table 9.34**: Floating lag time of formulation F1 after three months stability

| Sl.No | Formulation | Floating lag time |
|---|---|---|
| 1. | F1 | 36.00±0.005 |

**9.5.3.3.2 Total Floating time:**

The total floating time of tablet after three months study of stability was studied.

It was found to be more than(>) 12 hrs.

**9.5.3.4. *In vitro* Drug Release study:**

The Percentage Drug Release from F1 tablet after three months of stability was studied. The data is shown in Table 9.35.

**Table 9.35:** *In vitro* drug release data of formulation F1 at the end of three months of stability

| Sl. No. | Medium | Time (hours) | Amount of drug released (mg) | % Drug Release | %DE | MDT (hrs) |
|---|---|---|---|---|---|---|
| 1 | 0.1N HCl | 0 | 0.00 | 0 | 0.00 | 0.00 |
| 2 | | 1 | 1.08 | 7.27±0.035 | 0.01 | 0.50 |
| 3 | | 2 | 2.42 | 15.60±0.036 | 0.01 | 1.02 |
| 4 | | 3 | 3.76 | 23.94±0.026 | 0.02 | 1.52 |
| 5 | | 4 | 5.10 | 32.28±0.030 | 0.02 | 2.03 |
| 6 | | 5 | 6.44 | 40.62±0.040 | 0.03 | 2.54 |
| 7 | | 6 | 7.78 | 48.96±0.030 | 0.03 | 2.94 |
| 8 | | 7 | 9.12 | 57.30±0.040 | 0.04 | 3.48 |
| 9 | | 8 | 10.46 | 65.64±0.025 | 0.04 | 4.09 |
| 10 | | 9 | 11.80 | 73.98±0.030 | 0.05 | 4.82 |
| 11 | | 10 | 13.14 | 82.32±0.028 | 0.05 | 5.01 |
| 12 | | 11 | 14.48 | 90.66±0.045 | 0.06 | 5.34 |
| 13 | | 12 | 15.82 | 99.00±0.030 | 0.06 | 6.02 |

All the values are expressed as a mean ± SD., n = 3

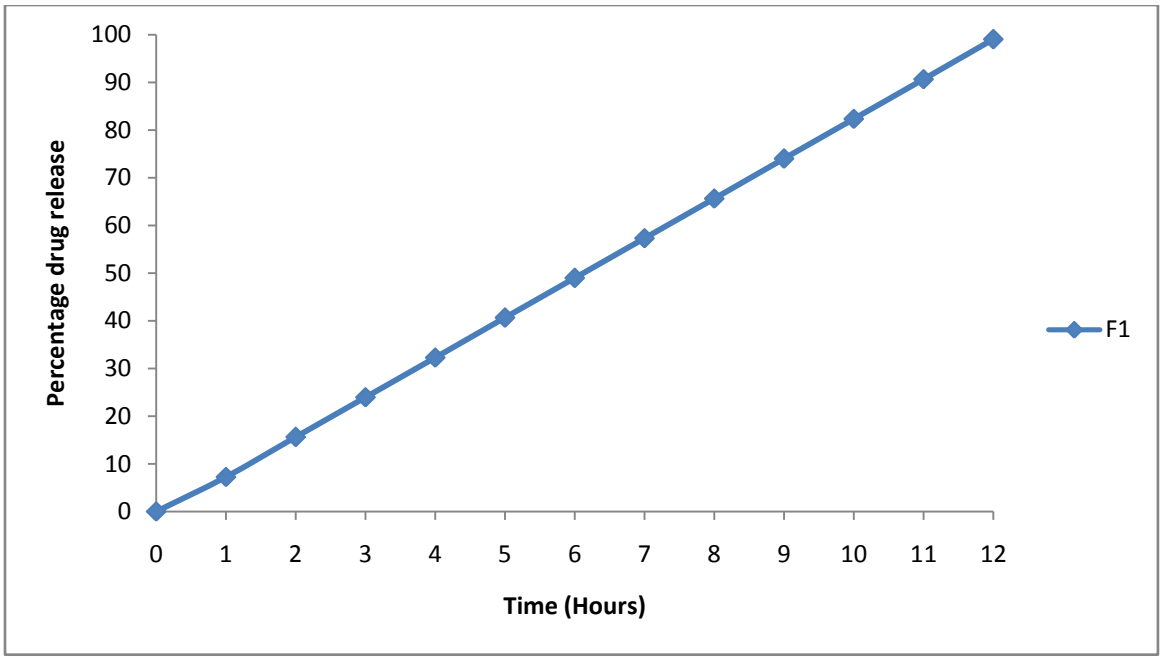



**Fig. 9.42:** *In vitro* drug release profile of formulation F1 at the end of 3 months of stability

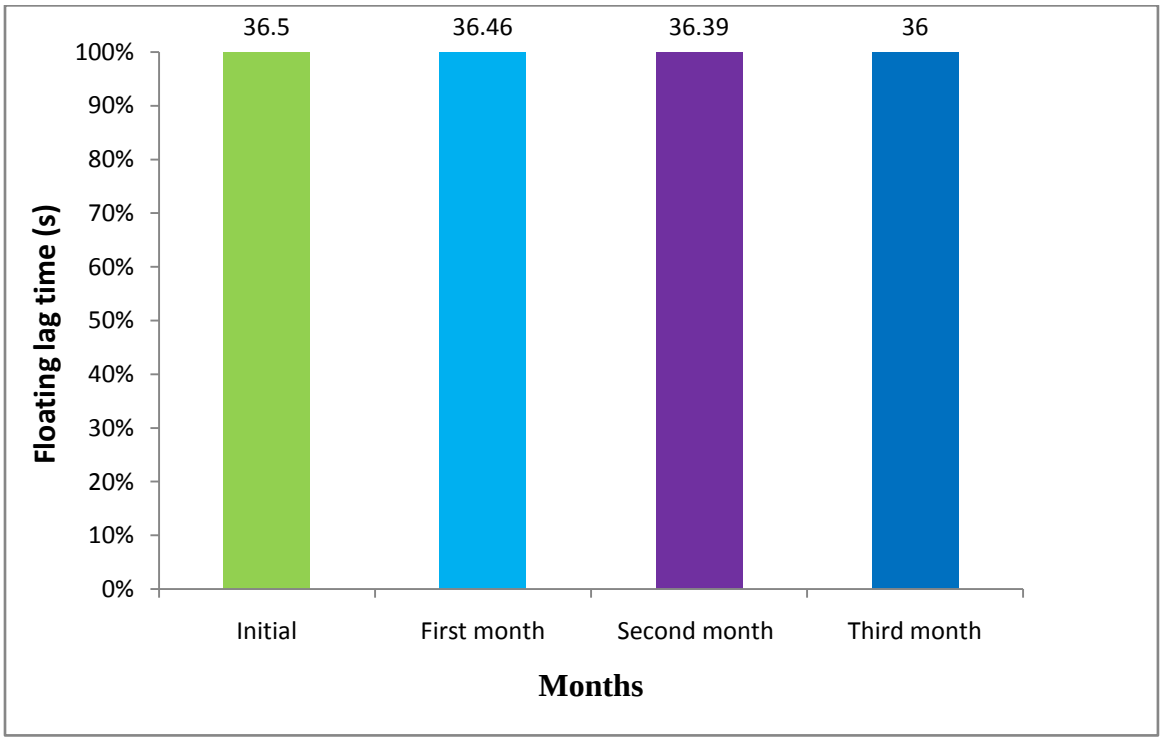



**Fig 9.43:** Floating lag time of F1 after stability studies for 3 months

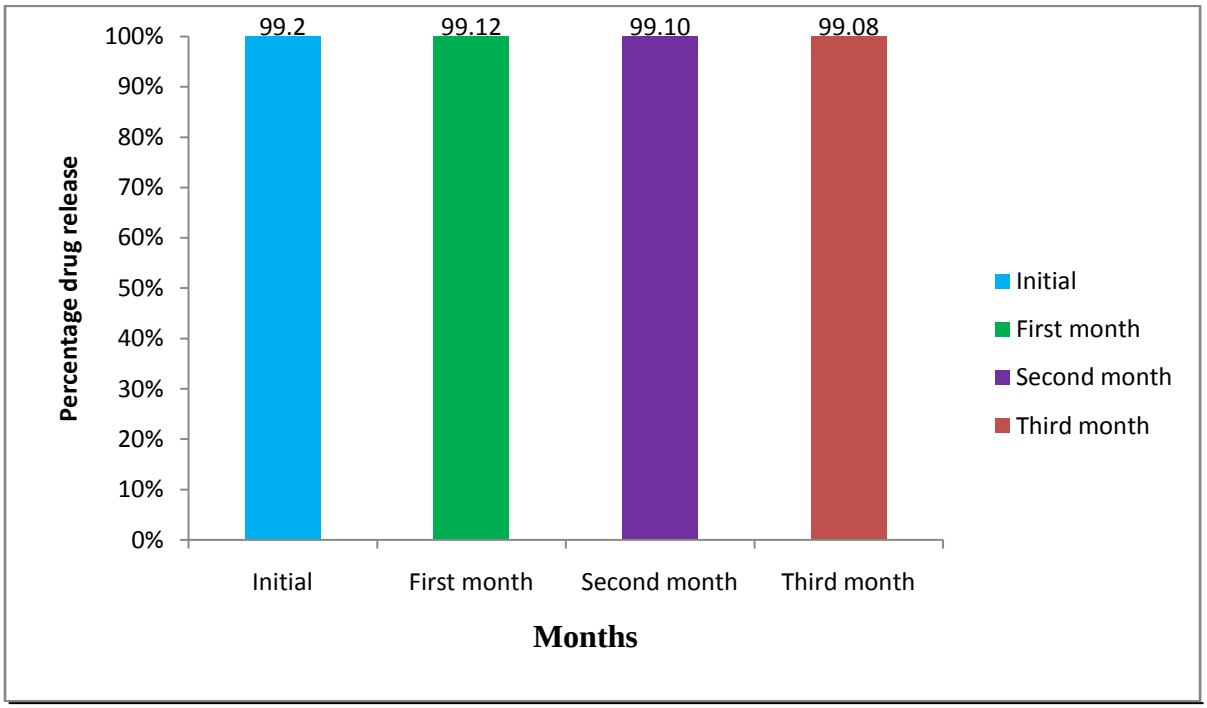



**Fig. 9.44**: Comparisons of percentage drug content for formulation F1 with initial and different periods of stability

No statistically significant differences were observed in Hardness, percentage drug content and percentage drug release in optimized formulation at the end of three months of stability studies.

So, it can be concluded that the formulation is stable for short term storage conditions.

# SUMMARY
# &
# CONCLUSION

# 10. SUMMARY AND CONCLUSION

The formulation development and in-vitro evaluation of gastroretentive floating drug delivery system of ofloxacin tablets was performed in the present study. The formulation development of intragastric floating drug delivery system of Ofloxacin in the form of tablets was performed by using $3^2$ full factorial method with polymers HPMC K15, HPMC K100 and SLS.

Preformulation study was carried out for powder blends, it was evaluated to determine the flow characteristics by angle of repose, bulk density, tapped density, carr's index and Hausner's ratio. The data obtained from these studies indicated that the powder blends had good flow properties.

The tablets were prepared with different ratios of polymers by direct compression technique. The formulated tablets were evaluated for physical characterization like thickness, hardness, friability, weight variation and drug content. All the physical parameters of prepared tablets compiles with IP specifications.

Evaluation studies of all formulations showed that the drug content, weight variation and friability as per the standards given in IP. The hardness of all formulations was within the limits.

The swelling index of the tablets of the tablets from each formulation was evaluated. The highest swelling was observed with the formulation F1. The amount of water uptake may be due to quick hydration of polymers.

The in-vitro dissolution study closely indicates that among nine formulations the formulation F1 showed high percentage of drug release and it is considered as the best formulation.

The regression correlation co-efficient value was concluded in kinetics modeling of drug dissolution profile for all formulations. The formulation F1 was found to be best fit model following peppas drug release.

From the stability data, it can be concluded that there was no significant changes in any parameters. Hence, the formulation F1 is considered to be highly stable formulation.

The overall studies indicate that polymers HPMC K15 and HPMC K100 and SLS (2%) showed satisfactory gastro retentive properties. Among the nine formulations the formulation F1exhibited optimum drug release profile.

Hence, it is concluded that the formulation F1 will be useful for preparing gastroretentive drug delivery system of Ofloxacin.

# FUTURE PROSPECTS

# 11. FUTURE PROSPECTS

In the present work floating tablets of Ofloxacin were formulated using synthetic polymers by direct compression method. In this work only physicochemical characterization, formulation and in-vitro evaluation of floating tablets of Ofloxacin was done. Along with in-vitro release study in-vivo release behavior of drug is also important. So in future in-vivo release study using different models are required to set the in-vitro in-vivo correlation which is necessary for development of successful formulation and also long term stability studies are necessary.

Convincing results for clinical studies have yet to be obtained for a gastroretentive system that displays the necessary performance behavior and which is retained in the fasted stomach of humans for a sensible period of time after dosing. Furthermore, the system will need to retain its integrity for an extended period of time in the harsh conditions present in the human stomach.

The control of GI transit profiles could be focus of the next two decades and might result in the availability of new products with new therapeutic possibilities and substantial benefits for patients.

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